

RESPONSE TO NOTICE OF NON-COMPLIANT AMENDMENT

Application No.: 10/551,475

Attorney Docket No.: Q111431

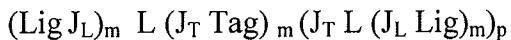
AMENDMENTS TO THE CLAIMS

This listing of claims will replace all prior versions and listings of claims in the application:

LISTING OF CLAIMS:

1-46. (Cancelled).

47. (currently amended). Library comprising a plurality of tagged ligands of formula I



and salts thereof wherein any optically active fluorescent ligand is present as a racemate or as one of its optically active isomers

comprising one or a plurality of same or different ligand moieties Lig each linked to one or a plurality of same or different tag moieties Tag via same or different linker moieties L and same or different linking site or linking functionality J_T and J_L

wherein Lig comprises a GPCR ligand, an inhibitor of an intracellular enzyme or a substrate or inhibitor of a drug transporter;

L is selected from a single or double bond, -O-, -S-, amine, COO-, amide, -NN-hydrazine; and saturated or unsaturated, substituted or unsubstituted C₁₋₆₀₀ branched or straight chain aliphatic, aromatic, alicyclic and combinations thereof, any of which may comprise one or more heteroatoms selected from N, O, S, P, wherein optional substituents are selected from any C₁₋₂₀ aliphatic, aromatic or alicyclic substituents any of which may comprise one or more heteroatoms as hereinbefore defined, hydroxy, thiol, halo, amine, hydrazine, oxo, cyano and carbonyl and combinations thereof, and L may be monomeric, oligomeric having oligomeric repeat of 2 to 30 or polymeric having polymeric repeat in excess of 30 up to 300;

Tag is any tagging substrate;

m are each independently selected from a whole number integer from 1 to 3;

p is 0 to 3

RESPONSE TO NOTICE OF NON-COMPLIANT AMENDMENT

Application No.: 10/551,475

Attorney Docket No.: Q111431

wherein one or more of each -Tag in one or more or each library compound is a fluorophore entity -Fl, whereby the library comprises compounds of which one or more or all of which are of formula I'

$(\text{Lig} J_L)_m L (J_T \text{Fl})_m (J_T L (J_L \text{Lig})_m)_p$

characterised in that linking is at same or different linking sites in compounds comprising different Lig, J_L , L J_T and/or - Tag and is at different linking sites in compounds comprising same Lig, J_L , L J_T and/or - Tag

wherein the or each Fl is selected from a red, near ir or blue dye with the proviso that when Lig is CGP12177 and L is 1,1,4,4 tetramethyl butylamine $C(CH_3)_2(CH_2)_2C(CH_3)_2NH$, Fl is not BODIPY® FL, or when L is $C(CH_3)_2(CH_2)_2C(CH_3)_2NHCSNH$ then Fl is not FITC, eosin or erythrosin.

48. (withdrawn and currently amended) Library comprising a plurality of tagged ligands of formula I

$(\text{Lig} J_L)_m L (J_T \text{Tag})_m (J_T L (J_L \text{Lig})_m)_p$

and salts thereof wherein any optically active fluorescent ligand is present as a racemate or as one of its optically active isomers

comprising one or a plurality of same or different ligand moieties Lig each linked to one or a plurality of same or different tag moieties Tag via same or different linker moieties L and same or different linking site or linking functionality J_T and J_L

wherein Lig comprises a GPCR ligand, an inhibitor of an intracellular enzyme or a substrate or inhibitor of a drug transporter;

L is selected from a single or double bond, -O-, -S-, amine, COO-, amide, -NN-hydrazine; and saturated or unsaturated, substituted or unsubstituted C_{1-600} branched or straight chain aliphatic, aromatic, alicyclic and combinations thereof, any of which may comprise one or more heteroatoms selected from N, O, S, P, wherein optional substituents are selected from any C_{1-20} aliphatic, aromatic or alicyclic substituents any of which may comprise one or more heteroatoms as hereinbefore defined, hydroxy, thiol, halo, amine, hydrazine, oxo, cyano and carbonyl and combinations thereof, and L may be monomeric, oligomeric having

RESPONSE TO NOTICE OF NON-COMPLIANT AMENDMENT

Application No.: 10/551,475

Attorney Docket No.: Q111431

oligomeric repeat of 2 to 30 or polymeric having polymeric repeat in excess of 30 up to 300;

Tag is any tagging substrate;

m are each independently selected from a whole number integer from 1 to 3;

p is 0 to 3

wherein one or more of each -Tag in one or more or each library compound is a fluorophore entity -Fl, whereby the library comprises compounds of which one or more or all of which are of formula I'

$(LigJ_L)_m L (J_T Fl)_m (J_T L (J_L Lig)_m)_p$

characterised in that linking is at same or different linking sites in compounds comprising different Lig, J_L, L J_T and/or – Tag and is at different linking sites in compounds comprising same Lig, J_L, L J_T and/or – Tag.

wherein the or each Fl is selected from the following dyes: Texas red™, coumarin and derivatives, Cascade Blue™, EvoBlue and fluorescent derivatives thereof, pyrenes and pyridyloxazole derivatives, the cyanine dyes, the dyomics (DY dyes and ATTO dyes) and fluorescent derivatives thereof, the Alexafluor dyes and derivatives, BDI dyes including the commercially available Bodipy™ dyes, pyrenes, anthracenes, acridines, fluorescent phycobiliproteins and their conjugates and fluoresceinated microbeads, and Texas Red derivatives, coupled to amine groups using the isocyanate, succinimidyl ester or dichlorotriazinyl-reactive groups.

49. (withdrawn and currently amended). Library as claimed in any of Claim 47 wherein each compound of formula I or I' comprises one of a plurality of fluorophores and/or tags providing a library of differently fluorescently tagged ligands comprising one or a number of different fluorophores optionally of different chemical composition or spectral characteristics; and/or providing a library of differently tagged ligands including at least one fluorescently tagged ligand; alternatively each compound of formula I or I' comprises one of a plurality of precursor ligands linked each to one or a plurality of different tags providing a library of same or differently tagged ligands of plural ligand type; alternatively each compound of formula I comprises one of a plurality of linkers linking a precursor ligand and at least one Tag at the same or different linking site; alternatively each compound of formula I or I' comprises the same

RESPONSE TO NOTICE OF NON-COMPLIANT AMENDMENT

Application No.: 10/551,475

Attorney Docket No.: Q111431

linker linking a precursor ligand and at least one Tag at different linking sites providing a library of differently linked tagged ligands of different conformation or anticipated pharmacology and binding.

50. (withdrawn). Library as claimed in Claim 47 comprising a plurality of compounds of one or more of formula II to III;

II $(\text{LigJ}_L)_m \text{ L J}_T \text{ TagJ}_T \text{ L (J}_L \text{ Lig)}_m$ where each m is as hereinbefore defined and is preferably 1 or 2, more preferably 1

III $(\text{LigJ}_L)_m L (\text{J}_T \text{Tag})_m$ wherein each m is as hereinbefore defined and is preferably 1 and/or 2, more preferably

Lig J_I – L – J_I. Tag and/or

Lig J_L – L – J_T Tag and/or Lig J_L – L – J_T Tag
 ↘J_L Lig ↘J_T Tag

wherein each J_L and J_T comprises J as hereinbefore defined and may be same or different and may derive from functionality originally present in Lig or L and Tag or L or a combination thereof, characterised in that linking is at same or different linking sites in compounds comprising different Lig, J_L , L, J_T and/or Tag, and is at different linking sites in the case of any two or more compounds comprising identical Lig, J_L , L, J_T and/or Tag.

51. (withdrawn). Library as claimed in Claim 47 including information for each compound of formula I comprised in the Library, relating to the pharmacology for binding to or inhibition of a GPCR receptor or to inhibition of an intracellular cyclic nucleotide phosphodiesterase, or inhibition of or transport by a drug transporter including designation as agonist, antagonist, substrate or inhibitor and measure of affinity or inhibition, enabling quantification of results.

52. (withdrawn). Library as claimed in Claim 47 wherein a GPCR ligand is selected from any compound which is effective as an agonist or antagonist for an adenosine receptor, a beta-adrenoceptor, a muscarinic receptor, a histamine receptor, an opiate receptor, a cannabinoid receptor, a chemokine receptor, an alpha-adrenoceptor, a GABA receptor, a prostanoid receptor,

RESPONSE TO NOTICE OF NON-COMPLIANT AMENDMENT

Application No.: 10/551,475

Attorney Docket No.: Q111431

a 5-HT (serotonin) receptor, an excitatory aminoacid receptor (glutamate), a dopamine receptor, a protease-activating receptor, a neurokinin receptor, an angiotensin receptor, an oxytocin receptor, a leukotriene receptor, a nucleotide receptor (purines and pyrimidines), a calcium-sensing receptor, a thyroid-stimulating hormone receptor, a neurotensin receptor, a vasopressin receptor, an olfactory receptor, a nucleobase receptor (adenosine), a lysophosphatidic acid receptor, a sphingolipid receptor, a tyramine receptor (trace amines), a free-fatty acid receptor and a cyclic nucleotide receptor; an inhibitor of intracellular enzymes is an inhibitor of cyclic nucleotide phosphodiesterases; and a substrate or inhibitor of a drug transporter is selected from a substrate or inhibitor of an equilibrium based drug transporter or ATP driven pump selected from a catecholamine transporter, a nucleoside transporter, an ATP-binding cassette transporter, a cyclic nucleotide transporter or derivatives or analogues thereof;

or wherein Lig is selected from

- a) xanthine like structures including XAC, theophylline, caffeine, theobromine, dyphilline, enprofylline; or fused biaryl structures including papaverine, dihydroquinilones, cilostamide, dipyridamole or vinpocetine; and analogues thereof;
- b) adenosine like structures including ADAC, NECA and analogues thereof;
- c) ethanolamine like structures including salmeterol, salbutamol, terbutaline, quinprenaline, labetalol, sotalol, bambuterol, fenoterol, reprotohol, tulobuterol, clenbuterol and analogues thereof;
- d) oxypropanolamine like structures including CGP12177, propranolol, practolol, acebutalol, betaxolol, ICI 118551, alprenolol, celiprolol (celectol), metoprolol (betaloc), CGP20712A, atenolol, bisoprolol, misaprolol, carvedilol, bucindolol, esmolol, nadolol, nebivolol, oxprenolol, xamoterol, pindolol, timolol and analogues thereof;
- e) xanthine like structures including XAC, theophylline, caffeine, theobromine, dyphilline, enprofylline, sildenafil, EHNA (erythro-9-(2-hydroxyl-3-nonyl)adenine), zaprinast; or spiro bicyclic structures including bypyridines, amrinone; imidazolines, CI930; dihydropyridazinones, indolan, rolipram, SB207499; or fused biaryl structures including papaverine, dihydroquinilones, cilostamide, dipyridamole, vinpocetine and analogues thereof.

53. (withdrawn). Library as claimed in Claim 47 wherein J_{Lm} L J_{Tm} comprises a mono, di, tri, tetra, penta, or hexa amino, alkylthio, alkoxy, carboxylic acid, and combinations thereof

RESPONSE TO NOTICE OF NON-COMPLIANT AMENDMENT

Application No.: 10/551,475

Attorney Docket No.: Q111431

including a mono, di or tri aminoalkylthio, amino alkoxy, alkoxy carboxylic acid or alkoxy amine, mono, di or tri amino methane, amino ethane, thio ethane, ethane, amino acyl, polypeptide, or mono or polyether derivatives including diamine or dithio derivatives, mono or polyethylene glycol di or tri amine or thio;

or comprises a mono-, di-, tri- or tetra, penta or hexafunctional linear or branched or cyclic substituted or unsubstituted hydrocarbyl of formula -L.I-

$J[A]q_L R_L [A'q_{L'} J']_p A''q_{L''} J''$

wherein each of J to J'' is a linking site or functionality as hereinbefore defined independently selected from a single or double bond, methylene, alkyne, alkene, NR, O, CONR, NRCO, S, CO, NCO, CHHal and P wherein R is H or C₁₋₈ alkyl or cycloalkyl or forms part of a cyclic ring with N, Hal is any halogen selected from chlorine, iodine, bromine; and is present in any rational location in a group A to A'';

each of A to A'' is a group selected from -O-, -C(=O)-, C₁₋₁₂ alkoxy, alkoyl, cycloalkyl, heterocyclic, alkyl, alkenyl, aryl, arylamide, arylamine, amino, thioalkyl, heteroaryl as hereinbefore defined and combinations thereof, optionally substituted by groups selected independently from C₁₋₃ alkyl and C₁₋₅ alkoxy;

each of q_L to q_{L''} are independently-selected from 0 or 1 or indicates an oligomeric repeat and is from 2 to 30, or indicates a polymeric repeat unit and is from 31 up to 300.

R_L is a C, N or S atom or is a CR_{L'}, NR_{L'}, alkyl, cycloalkyl, heterocyclic, aryl heteroaryl, amine or thio moiety and provides for branching when p is 1 or 2; wherein R_{L'} is H or C₁₋₃ alkyl; and

p is as hereinbefore defined and is 0, 1 or 2.

54. (withdrawn). Library as claimed in Claim 47 wherein J_{Lm} L J_{Tm} is of formula

$J A q_L R_L J''$

wherein each of J and J'' is amine or -O-, A is CH₂CH₂O, q_L is 1-30 or 31 to 300 and R_L is CH₂CH₂

or of formula

$J A q_L R_L (A'J') J''$

RESPONSE TO NOTICE OF NON-COMPLIANT AMENDMENT

Application No.: 10/551,475

Attorney Docket No.: Q111431

wherein each of J, J' and J'' independently is amine, -O or a single bond, q_L is 1, 2 or 3 -30 or 31 to 300 and A is CH₂CH₂O or HNCH₂CO or q_L is 1 and A is C(O) or (CH₂)₁₋₈ or q_L is 0, R_L is CH or CH₂CH, q_{L'} is 0 or q_{L'} is 1 and A' is CH₂ and q_{L''} is 0

preferably

O(CH₂CH₂O)_{qL}CH₂CH₂NH, O(CH₂CH₂O)_{qL}CH₂CH(CH₂NH)NH,
OCH(CH₂NH)NH, -CH(CH₂NH)NH, -C(O) NH-, -(CH₂)₁₋₈- or (-HNCH₂CO-)₁₋₃ (= -gly₁₋₃-) -.

55. (withdrawn). Library as claimed in Claim 47 wherein each compound of formula I or I' comprises a moiety Lig and L as hereinbelow defined:

Wherein:

any optically active fluorescent ligand is present as a racemate or as one of its optically active isomers

Lig.a_m is suitably of the formula, in either of the following forms given, including any of its possible linking configurations or sites:



Lig.a¹_m

Wherein at least one or all of Ra¹ to Ra⁴, X¹ and X² comprise a linking site or functionality J as hereinbefore defined

X¹ and X² are each independently selected from H, O, OR.a, NR.a, NHR.a;

X¹ and X² are each preferably O;

each of R.a¹, R.a², R.a³ and R.a⁴ independently is selected from H or C₁₋₄ linear or branched alkyl optionally mono or multi hydroxy or halo substituted;

R.a⁴ is selected from a heteroatom O, S or substituted or unsubstituted amine or saturated or unsaturated, substituted or unsubstituted C₁₋₂₀ branched or straight chain aliphatic,

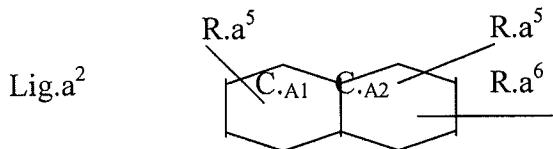
RESPONSE TO NOTICE OF NON-COMPLIANT AMENDMENT

Application No.: 10/551,475

Attorney Docket No.: Q111431

aromatic, alicyclic and combinations thereof, any of which may comprise one or more heteroatoms selected from N, O, S, P; wherein optional substituents are selected from any C₁₋₁₂ aliphatic, aromatic or alicyclic substituents any of which may comprise one or more heteroatoms as hereinbefore defined, hydroxy, thiol, halo, amine, hydrazine, oxo and cyano; including optionally substituted aryl, cycloalkyl, alkyl, ketone, (di)amine, (di)amide, alkoxy, cycloalkyl, carboxylic acid or optionally o-, m- or p- substituted phenyl wherein substituents include aryl, alkyl, cycloalkyl, heteroaryl or heteroalkyl, amine, amide, carboxyl, carbonyl or R.a⁴ comprises cyclohexyl, cyclopentyl, ethoxy, (CH₂)₂PhPh, CH₂Ph, CONH(CH₂)_nCONH, CH₂CONH(CH₂)₂NH, CH₂PhNHCOCH₂, CH₂CH₂OCOCH₂, succinimidyl ester, NHCOCH₂, CH₂(CH₃)NCOCH₂, H₂N(CH₂)₂NHCOCH₂, H₂N(CH₂)₈NHCOCH₂, H₂NNHCOCH₂, CH₂CONH(CH₂)₂NHCOCH₂, HOPhCH₂N(CH₂CH₃.HOAc)(CH₂)₂NHCOCH₂, heterocyclic-(CH₂)₄CONH(CH₂)₂NHCOCH₂ or heterocyclic-NHCON(heterocyclic)COCH₂;

or Lig.a is of the formula Lig.a²-



wherein at least one or all of Ra⁵ to Ra⁶, or a cyclic C or heteroatom comprise a linking site or functionality J as hereinbefore defined, each of C._{A1} and C._{A2} is independently selected from C₅₋₆ aryl, heteroaryl, cycloalkyl and heterocyclic, more preferably from phenyl, or aryl containing 1 or 2 ring heteroatoms, or heterocyclic containing 1 ring heteroatom and/or 1 ring -C=C- group; Each of up to seven R.a⁵ is a substituent of a ring carbon or a ring heteroatom and:

is independently selected from H, halo, hydroxy, thiol, amine, COOH, hydrazine, cyano, saturated or unsaturated, substituted or unsubstituted C₁₋₂₀ branched or straight chain aliphatic, aromatic, alicyclic and combinations thereof, any of which may comprise one or more heteroatoms selected from N, O, S, P, and wherein optional substituents are selected from any C₁₋₁₂ aliphatic, aromatic or alicyclic substituents any of which may comprise one or more heteroatoms as hereinbefore defined, hydroxy, thiol, halo, amine,

RESPONSE TO NOTICE OF NON-COMPLIANT AMENDMENT

Application No.: 10/551,475

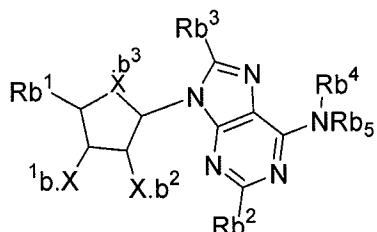
Attorney Docket No.: Q111431

hydrazine, oxo =O or cyano; OCH₃, CH₂Ph(OCH₃)₂, O(CH₂)₃CON(CH₃)c.hex, N(CH₂CH₂OH)₂, c.hex, COOCH₂CH₃, CH₂CH₃;
 or any two or more of R.a⁵ form a one, two or three ring fused cyclic structure, a fused 3 ring aryl, 5-heterocyclic or 6-heterocyclic structure having 4 ring atoms common with the fused bicyclic Lig.a² structure;
 and R.a⁶ is a moiety as defined for R.a⁵ above;

and L.a is as hereinbefore defined for L or J_L L J_T or L.I or subformulae as hereinbefore defined, or is a single bond, amino acid or amide including a peptide or polypeptide gly or gly₃, alkyl of formula -(CH₂)_n where n is 3 to 8, optionally including one or more heteroatoms or unsaturated groups, including -O- or -S- or -CH=CH-:

Lig.b is suitably of the formula Lig.b including any of its possible linking configurations or sites:

Lig.b



wherein at least one or all of Rb¹ to Rb⁵ or Xb¹ to Xb³ comprise a linking site or functionality J as hereinbefore defined

ring substituents X.b¹ and X.b² are independently selected from hydrocarbon including alkyl or SR_X, NR_{X.2} and OR_X wherein (each) R_X is selected from H, C₁₋₅alkyl, alkenyl;
 ring heteroatom X.b³ is selected from -S-, -O- and -CH₂-;

Rb¹ is selected from saturated or unsaturated, substituted or unsubstituted C₁₋₄ aliphatic, or C₁₋₃ alicyclic optionally including one or more heteroatoms N, O, S, P, wherein substituent(s) are selected from one or more cycloalkyl, heterocyclic, hydroxy, oxo, halo, amine; or R.b¹ comprises a carbonyl substituted by H, alkyl or

RESPONSE TO NOTICE OF NON-COMPLIANT AMENDMENT

Application No.: 10/551,475

Attorney Docket No.: Q111431

a linear or cyclic primary, secondary or tertiary amine, substituted C₁₋₃ alkyl, cycloalkyl or amide, cyclopropyl, or CONHC₁₋₃alkyl including CONHET or CH₂OH

and each of R.b² and R.b³ is selected from H, halo, hydroxy, thiol, amine, COOH, CHO, hydrazine, cyano or saturated or unsaturated, substituted or unsubstituted C₁₋₂₀ branched or straight chain aliphatic, aromatic, alicyclic and combinations thereof, any of which may comprise one or more heteroatoms selected from N, O, S, P; wherein optional substituents are selected from any C₁₋₁₂ aliphatic, aromatic or alicyclic substituents any of which may comprise one or more heteroatoms as hereinbefore defined, hydroxy, thiol, halo, amine, hydrazine, oxo or cyano, preferably from H, halo or hydroxy;

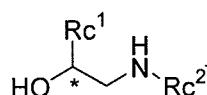
Rb⁴ is H;

Rb⁵ is H or alkyl

L.b comprises a linking site or functionality J as hereinbefore defined; and is as hereinbefore defined for L or its subformulae, more preferably is saturated and unsaturated substituted or unsubstituted C₁₋₁₂ aliphatic or C₁₋₂₄ aromatic as defined for L optionally including one or more heteroatoms O, S or N, cyclic or heterocyclic groups, or is of formula L.I or its subformulae as hereinbefore defined, or is (CH₂)_m wherein m is 2 to 12, or is (Ph-CH₂CONH)₂ (CH₂)₂;

Lig.c is of the formula Lig.c including any of its possible linking configurations or sites:

Lig.c HOC*(R.c¹)CH₂NH-R.c²



where at least one or all of Rc¹ to Rc² or OH, or a chain C or N comprise a linking site or functionality J as hereinbefore defined

* indicates an optically active centre and

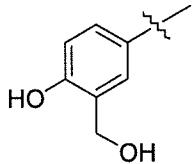
wherein R.c¹ is C₆₋₁₄ aryl optionally including one or more heteroatoms selected from H, O, optionally substituted by OH, Hal, NH₂, NHC₁₋₃alkyl, sulphonamide, oxoamine or

RESPONSE TO NOTICE OF NON-COMPLIANT AMENDMENT

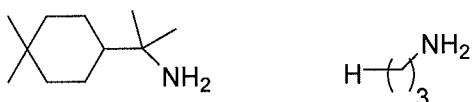
Application No.: 10/551,475

Attorney Docket No.: Q111431

(-CONH₂), or is mono, di or tri substituted phenyl or quinoline wherein substituents include OH, Cl or NH₂, or is m-CH₂OH, p-OH phenyl, m-,p-dihydroxy phenol or m-,m-dihydroxyphenol, m-,m-diCl, p-NH₂ phenol, p-OH, m-CONH₂ phenol or 5-OH, 8-quinoline,



R.c² is selected from saturated or unsaturated, substituted or unsubstituted C₁₋₂₀ branched or straight chain aliphatic, aromatic, alicyclic and combinations thereof, any of which may comprise one or more heteroatoms selected from N, O, S, P; wherein optional substituents are selected from any optionally substituted C₁₋₁₂ aliphatic, aromatic or alicyclic substituents any of which may comprise one or more heteroatoms as hereinbefore defined, hydroxy, thiol, halo, amine, hydrazine, oxo or cyano and combinations thereof; or R.c² is selected from C₁₋₆ branched or straight chain aliphatic, C₆₋₁₀ araliphatic optionally substituted by OH and optionally including heteroatoms selected from N,O, optionally including an ether O, and is selected from -(CH₂)₆OCH((CH₂)₃Ph), CHCH₃(CH₂)₂Ph, CHCH₃CH₂PhOH, C(CH₃)₂CH₂Ph or from the structures:



L.c is present as R.c² or comprises a linking site or functionality J as hereinbefore defined, and is as hereinbefore defined for L, formula L.I or its subformulae as hereinbefore defined, or is selected from C₁₋₁₂ alkyl, amide;

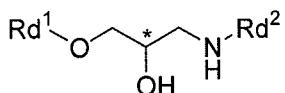
Lig.d is of the formula Lig.d including any of its possible linking configurations or sites:

Lig.d R.d¹ OCH₂C*HOHCH₂NH-R.d²

RESPONSE TO NOTICE OF NON-COMPLIANT AMENDMENT

Application No.: 10/551,475

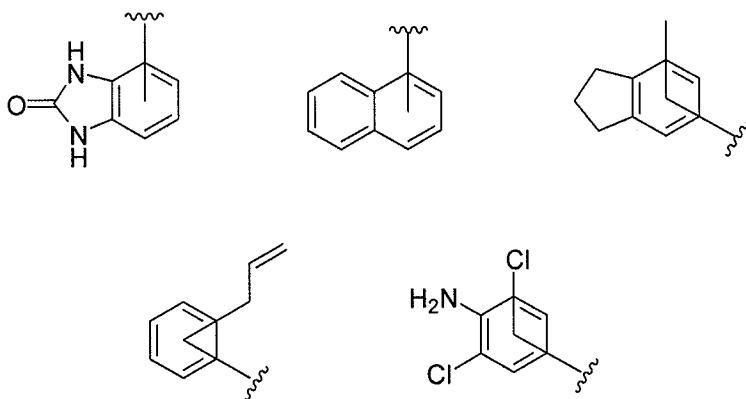
Attorney Docket No.: Q111431



wherein at least one or all of Rd¹ to Rd² or OH, a chain C or N comprise a linking site or functionality J as hereinbefore defined

* indicates an optically active centre

wherein R.d¹ is saturated or unsaturated, substituted or unsubstituted C₁₋₂₀ branched or straight chain aliphatic, aromatic, alicyclic and combinations thereof, any of which may comprise one or more heteroatoms selected from N, O, S, P; wherein optional substituents are selected from any C₁₋₁₂ aliphatic, aromatic or alicyclic substituents any of which may comprise one or more heteroatoms as hereinbefore defined, hydroxy, thiol, halo, amine, hydrazine, oxo or cyano; or R.d¹ is substituted or unsubstituted C₁₋₂₄ aralkyl or heteroaralkyl, including single ring and fused ring systems with (hetero)aryl or cycloalkyl rings, wherein optional substituents include C₁₋₆ alkyl, alkoxy, ether, carbonyl, alkenyl, amine, amide each optionally carbonyl, amide, halo or OH substituted, or halo or OH, amine, amide, carbonyl, ketone, ether substituted phenyl or naphthyl, mono-, di-, tri- or tetra substituted mono or polycyclic fused aryl or cycloaryl or heterocycloaryl including phenyl, carbazole or structures shown below or spiro ring systems, mono-, di-, tri- or tetra alkoxyalkyl, alkoxyalkoxyalkyl or CF₃ substituted phenyl or unsubstituted or monosubstituted naphthalene or 5,6 ring systems:

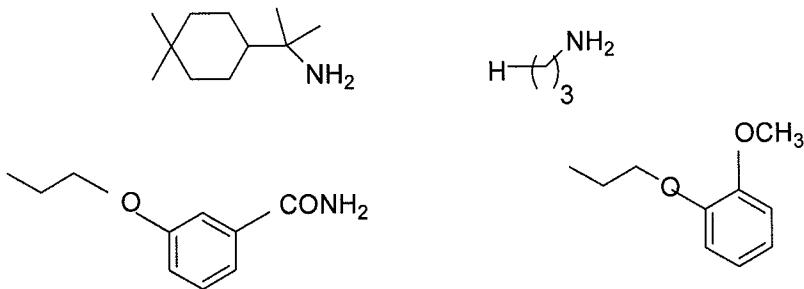


RESPONSE TO NOTICE OF NON-COMPLIANT AMENDMENT

Application No.: 10/551,475

Attorney Docket No.: Q111431

R.d² is substituted or unsubstituted amine, saturated or unsaturated, substituted or unsubstituted C₁₋₁₂ branched or straight chain aliphatic, aromatic, alicyclic and combinations thereof, any of which may comprise one or more heteroatoms selected from N, O, S, P; wherein optional substituents are selected from any C₁₋₁₂ aliphatic, aromatic or alicyclic substituents any of which may comprise one or more heteroatoms as hereinbefore defined, hydroxy, thiol, halo, amine, hydrazine, oxo or cyano, more preferably amine, C₁₋₆ branched or straight chain alkyl optionally including ether O, and optionally substituted by C₆₋₁₀ aryl, or of the formula:



L.d may be present as R.d² or may comprise a linking site or functionality J as hereinbefore defined and is as hereinbefore defined for L and its subformulae , formula L.I and its subformulae as hereinbefore defined, or is a single bond or is as hereinbefore defined for L.a;

Lig.e comprises a cell permeant moiety or is associated with a cell permeant L or Fl moiety or is of the formula , in either of the following forms given including any of its possible linking configurations or sites:

RESPONSE TO NOTICE OF NON-COMPLIANT AMENDMENT

Application No.: 10/551,475

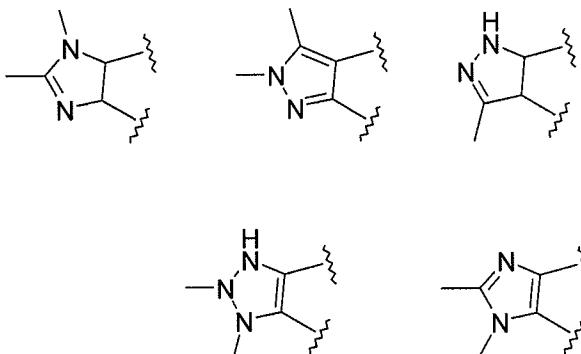
Attorney Docket No.: Q111431

Lig.e¹

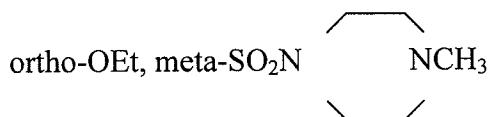


wherein at least one or all of Re¹ to Re⁴, X and a ring C or N comprise a linking site or functionality J as hereinbefore defined

h is selected from



each optionally substituted by R.e³ – R.e⁴ wherein R.e¹ – R.e⁴ are as R.a¹ – R.a⁴ defined above or in which R.e³ is C₅₋₉ linear or branched alkyl, optionally mono or multi hydroxy or halo substituted or is aryl optionally substituted by alkoxy or sulfonyl,



each X is independently selected from H, O, -OR.e², N, HN, NR.e⁵, HR.e⁶, and aryl optionally substituted by ether; or X is aryl optionally alkyl or alkoxy substituted or is Ph-ortho-OCH₂CH₂CH₃;

RESPONSE TO NOTICE OF NON-COMPLIANT AMENDMENT

Application No.: 10/551,475

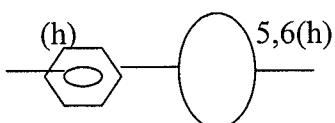
Attorney Docket No.: Q111431

and where R.e⁵ is as defined above for R.e¹ above or forms a fused cyclic ring together with the adjacent ring N atom, or 1 or 2 fused 5 membered cyclic rings;

and R.e⁶ is as defined above for R.e¹ above or is selected from optionally substituted phenyl wherein optional substituents include ether, o-ethoxy or o-propoxy, alkyl or OH, sulphonyl or carbonyl substituted by heterocyclic, or cyclic C₅₋₈ alkyl, piperazinyl or sulphonyl;

or Lig.e is of the formula Lig.e²

Lig.e²



wherein at least one or all free ring atom or their substituents comprise a linking site or functionality J as hereinbefore defined

each spiro ring optionally comprises zero or one or more heteroatoms h

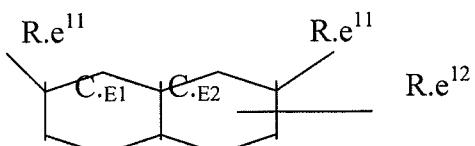
or (h) comprises zero or 1 N

heteroatom and 5,6(h) comprises zero, 1 or 2 N heteroatoms and is unsaturated or comprises one or two -C=C- or -C=N- groups;

and wherein each ring is optionally substituted by one or more oxo, CO, COOH, C₁₋₆ alkyl or linear or cyclic alkoxy optionally substituted by one or more oxo, CO, COOH, CN, or C₁₋₆ alicyclic or amine groups, amine or one or more spiro or fused heterocycles;

or Lig.e is of the formula Lig.e³

Lig.e³



RESPONSE TO NOTICE OF NON-COMPLIANT AMENDMENT

Application No.: 10/551,475

Attorney Docket No.: Q111431

wherein at least one or all of Re¹¹ to Re¹², or a ring C or heteroatom or ring substituent comprise a linking site or functionality J as hereinbefore defined

each of C._{E1} and C._{E2} is independently selected from C₅₋₆ aryl, heteroaryl, cyloalkyl and heterocyclic, including phenyl, or aryl containing 1 or 2 ring heteroatoms, or heterocyclic containing 1 ring heteroatom and/or 1 ring –C=C- group;

each of up to seven R.e¹¹ is a substituent of a ring carbon or a ring heteroatom and:

is independently selected from saturated or unsaturated, substituted or unsubstituted C₁₋₂₀ branched or straight chain aliphatic, aromatic, alicyclic and combinations thereof, any of which may comprise one or more heteroatoms selected from N, O, S, P, and wherein optional substituents are selected from any C₁₋₁₂ aliphatic, aromatic or alicyclic substituents any of which may comprise one or more heteroatoms as hereinbefore defined, hydroxy, thiol, halo, amine, hydrazine, oxo =O, or cyano, OCH₃, CH₂Ph(OCH₃)₂, O(CH₂)₃CON(CH₃)c.hex, N(CH₂CH₂OH)₂, c.hex, COOCH₂CH₃, CH₂CH₃;

or any two or more of R.e¹¹ form a one, two or three ring fused cyclic structure, a fused 3 ring aryl, 5-heterocyclic or 6-heterocyclic structure having 4 ring atoms common with the fused bicyclic Lig.e³ structure;

and R.e¹² is a moiety as defined for R.e¹¹ above;

L.e comprises a linking site or functionality J as hereinbefore defined and is suitably as hereinbefore defined for L.a.

56. (canceled)

57. (withdrawn). Library as claimed in Claim 56 wherein Fl is of formula J_T – t – Fl and comprises a BODIPY ™ structure characterised by a dipyrrometheneboron difluoride core, optionally modified by one or two fused rings, optionally substituted by one or several substituents selected from alkyl, alkoxy, aryl or heterocyclic, wherein one substituent –t- is adapted for linking as hereinbefore defined to a ligand precursor as hereinbefore defined,

RESPONSE TO NOTICE OF NON-COMPLIANT AMENDMENT

Application No.: 10/551,475

Attorney Docket No.: Q111431

wherein the substituent -t- comprises a proximal unsaturated or aryl moiety, comprising a medial short, medium or long chain alkynyl or cycloalkyl moiety and comprising a moiety derived from linking via a reactive group as hereinbefore defined or selected from carboxyl, sulphonate or as a heteroatom O or S or methylene derived from linking at an alkylhalide including methylbromide, haloacetamide or sulphonate ester electrophilic group.

58. (canceled)

59. (withdrawn and currently amended). Process for the preparation of a library as claimed in ~~ef~~-Claim 47 which is a combinatorial process; and comprises the reaction of one or more ligand precursors of formula IV and/or IV'

IV $(\text{LigJ}_L)_m - L - Y_{Lm}$

IV' Lig $Y_{\text{Lig}m}$

comprising one or more or different reactive groups Y_L or Y_{Lig} forming a linking functionality J , J_L or J_T as hereinbefore defined

with one or more of a plurality of analytical tagging substrates of formula V and/or V'

V $Y_{Tm} \text{ Tag}$

V' $Y_{Tm} L (J_T \text{ Tag})_m$

comprising one or more or different reactive groups Y_T forming a linking functionality J or J_T as hereinbefore defined

and optionally one or more linking species VI or VI' or VI''

VI $Y_{Lm} L Y_{Lm}$

wherein Lig, J, L, J_T and Tag and each m is independently as hereinbefore defined

wherein the or each compound of formula IV or IV' is capable of reaction with the or each compound of formula V or V', optionally via the or each species VI or VI' or VI'' to form a plurality of compounds of formula I as hereinbefore defined;

wherein linking is at same or different reactive sites in different compounds as hereinbefore defined.

RESPONSE TO NOTICE OF NON-COMPLIANT AMENDMENT

Application No.: 10/551,475

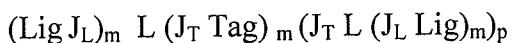
Attorney Docket No.: Q111431

60. (withdrawn and currently amended). Process for the preparation of a compound of formula I as hereinbefore hereinbelow defined in Claim 47-64 comprising the reaction of a compound of formula IV or IV' and a compound of formula V or V' and optionally additionally VI, as hereinbefore defined in claim 59, by reacting the unprotected primary alkyl amine group of a compound of formula IV with a compound of formula V comprising a reactive succinimidyl ester group in solvent at ambient temperature without the need for subsequent deprotection.

61-62. (canceled).

63. (withdrawn and currently amended). Method-Process as claimed in Claim 62 59 which comprises additionally determining pharmacology for a plurality of or all compounds in the library in order to enable selecting a compound exhibiting desired pharmacology, whereby the process comprises preparing a preliminary library of compounds, conducting screens to assess binding or inhibition, selecting a compound identified in the screen as having beneficial properties, and modifying or functionalising by nature of moieties or linking location of linking on the basis of the indications from the screen to prepare an optimised library, wherein the molecular pharmacology and photochemistry from the screen feedback into the design of the library.

64. (currently amended). A compound of formula I



or salt thereof wherein an optically active ligand is present as a racemate or as one of its optically active isomers

comprising ligand moiety Lig linked to tag moiety Tag via linker moiety L at linking site or linking functionality J_T and J_L

wherein Lig comprises a GPCR ligand, an inhibitor of an intracellular enzyme or a substrate or inhibitor of a drug transporter;

L is selected from a single or double bond, -O-, -S-, amine, COO-, amide, -NN-hydrazine; and saturated or unsaturated, substituted or unsubstituted C₁₋₆₀₀ branched or straight chain aliphatic, aromatic, alicyclic and combinations thereof, any of which may comprise one or more heteroatoms selected from N, O, S, P, wherein optional substituents are selected from any C₁₋₂₀ aliphatic, aromatic or

RESPONSE TO NOTICE OF NON-COMPLIANT AMENDMENT

Application No.: 10/551,475

Attorney Docket No.: Q111431

alicyclic substituents any of which may comprise one or more heteroatoms as hereinbefore defined, hydroxy, thiol, halo, amine, hydrazine, oxo, cyano and carbonyl and combinations thereof, and L may be monomeric, oligomeric having oligomeric repeat of 2 to 30 or polymeric having polymeric repeat in excess of 30 up to 300;

m are each independently selected from a whole number integer from 1 to 3;

p is 0 to 3

wherein -Tag is a fluorophore entity -Fl, whereby the compound is of formula I'

(LigJ_L)_m L (J_T Fl)_m (J_T L (J_L Lig)_m)_p

characterised in that Fl is selected from a red, near ir or blue dye

with the proviso that:

a) when Lig is XAC ie in Lig.a when each of R.a¹ and R.a² is propyl, R.a³ is H and R.a⁴ is -Ph-OCH₂CONH(CH₂)₂NH-, and L is a single bond Fl is not BODIPY™ 630/650 X; or

b) when Lig is ABEA, ie m is 4 and L is a single bond Fl is not BODIPY™ 630/650 X as hereinbefore defined in Claim 47 wherein J_L, L, T_{Tm} is of formula

J-Aq_L-R_L-J''

wherein each of J and J'' is amine or O, A is CH₂CH₂O, q_L is 1-30 or 31 to 300 and R_L is CH₂CH₂

or of formula

J-Aq_L-R_L(A'J')-J''

wherein each of J, J' and J'' independently is amine, O or a single bond, q_L is 1, 2 or 3-30 or 31 to 300 and A is CH₂CH₂O or HNCH₂CO or q_L is 1 and A is C(O) or (CH₂)₁₋₈ or q_L is 0, R_L is CH or CH₂CH, q_L is 0 or q_L' is 1 and A' is CH₂ and q_L'' is 0

preferably

O(CH₂CH₂O)_{q_L}CH₂CH₂NH, O(CH₂CH₂O)_{q_L}CH₂CH(CH₂NH)NH,

OCH(CH₂NH)NH, CH(CH₂NH)NH, -C(O) NH-, -(CH₂)₁₋₈ or (-HNCH₂CO)₁₋₃ (= gly₁₋₃-) and wherein any optically active fluorescent ligand is present as a racemate or as one of its optically active isomers.

65. (currently amended). A compound of formula I as defined in Claim 64 which is a compound of formula II or III as hereinbefore defined in Claim 50

II (LigJ_L)_m L J_T TagJ_T L (J_L Lig)_m where each m is as hereinbefore defined and is preferably 1 or 2, more preferably 1

RESPONSE TO NOTICE OF NON-COMPLIANT AMENDMENT

Application No.: 10/551,475

Attorney Docket No.: Q111431

III $(\text{LigJ}_L)_m L (J_T \text{Tag})_m$ wherein each m is as hereinbefore defined and is preferably 1 and/or 2, more preferably

Lig J_L – L – J_L Tag and/or

Lig J_L – L – J_T Tag and/or Lig J_L – L – J_T Tag
 ↘J_L Lig ↘J_T Tag

~~as hereinbefore defined in Claim 50 and wherein any optically active fluorescent ligand is present as a racemate or as one of its optically active isomers.~~

66. (currently amended). A compound according to Claim 64, wherein F1 is of formula J_T-t
- F1 and comprises a BODIPY™ structure characterised by a dipyrrometheneboron difluoride core, optionally modified by one or two fused rings, optionally substituted by one or several substituents selected from alkyl, alkoxy, aryl or heterocyclic, wherein one substituent -t- is adapted for linking as hereinbefore defined to a ligand precursor as hereinbefore defined, wherein the substituent -t- comprises a proximal unsaturated or aryl moiety, comprising a medial short, medium or long chain alkynyl or cycloalkyl moiety and comprising a moiety derived from linking via a reactive group as hereinbefore defined or selected from carboxyl, sulphonate or as a heteroatom O or S or methylene derived from linking at an alkylhalide including methylbromide, haloacetamide or sulphonate ester electrophilic group. Lig comprises a GPCR ligand, an inhibitor of an intracellular enzyme or a substrate or inhibitor of a drug transporter or F1 is a fluorophore entity, with the proviso that when Lig is CGP12177 and L is 1,1,4,4-tetramethyl butylamine C(CH₃)₂(CH₂)₂C(CH₃)₂NH, F1 is not BODIPY® FL, or when L is C(CH₃)₂(CH₂)₂C(CH₃)₂NHCSNH then F1 is not FITC, eosin or erythrosin characterised in that the or each F1 is selected from a red, near ir or blue absorbing dye or from BODIPY® 630/650 or BODIPY® 630/650 X.

67. (currently amended). A compound of the formula I or I' as hereinbefore defined in Claim 56-55 selected from formulae Lig. a_m L.a-Fl. a_n to Lig. e_m L.eFl. e_n as hereinbefore defined with the proviso that:

RESPONSE TO NOTICE OF NON-COMPLIANT AMENDMENT

Application No.: 10/551,475

Attorney Docket No.: Q111431

a) when Lig is XAC ie in Lig.a when each of R.a¹ and R.a² is propyl, R.a³ is H and R.a⁴ is -Ph-OCH₂CONH(CH₂)₂NH-, and L is a single bond or L is gly and n=3 or L is NCS, Fl is not fluorescein; or

when Lig is XAC and L is a single bond or NCS, Fl is not fluorescein or NBD;

b) when Lig is adenosine Fl is not Fmoc (CA 134:204756); or

when Lig is ADAC , ie R.b¹ is CH₂OH, R.b² and R.b³ are H and L is -(Ph-CH₂CONH)₂(CH₂)₂ or L is a single bond, Fl is not fluorescein, NBD or Rhodamine; or

when Lig is NECA (incorporating the moiety (CH₂)_m) ie R.b² and R.b³ are H and L is a single bond, or is (CH₂)_m when m is 2,4,6,8 or 10 then Fl is not NBD, or when m is 3,4,6,8,10 or 12 then Fl is not dansyl; or

when Lig is N⁶-[2-(4 aminophenyl)ethyl]adenosine and L is (CH₂)₂PhNH, Fl is not FITC (CA 131:56155 (8))

d) when Lig is CGP12177 and L (R.d²) is mono amine menthane, Fl is not BODIPY® TMR; or

when Lig is CGP12177 and L is 1,1,4,4 tetramethyl butylamine, i.e C(CH₃)₂(CH₂)₂C(CH₃)₂NH Fl is not BODIPY® FL, or when L is C(CH₃)₂(CH₂)₂C(CH₃)₂NHCSNH then Fl is not FITC, eosin or erythrosin; or when L is monoamine menthane, Fl is not FITC (CA 131:56155 (4)); or

when Lig is CGP12177 and L is a single bond, Fl is not NBD; or

when Lig is alprenolol i.e o-prop-2-enyl phenyl and L is -C(CH₃)₂- or a single bond, Fl is not NBD;

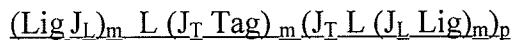
and a) e) when L is a single bond, Fl is not BODIPY FL;

optionally additionally

a) when Lig is XAC ie in Lig.a when each of R.a¹ and R.a² is propyl, R.a³ is H and R.a⁴ is -Ph-OCH₂CONH(CH₂)₂NH-, and L is a single bond Fl is not BODIPY™ 630/650 X; or

b) when Lig is ABEA, ie m is 4 and L is a single bond Fl is not BODIPY™ 630/650 X.

68. (currently amended). A compound of the formula I



or salt thereof and salts thereof wherein an optically active ligand is present as a racemate or as one of its optically active isomers

RESPONSE TO NOTICE OF NON-COMPLIANT AMENDMENT

Application No.: 10/551,475

Attorney Docket No.: Q111431

comprising ligand moiety Lig linked to tag moiety Tag via linker moiety L at linking site or linking functionality J_T and J_L

wherein Lig comprises a GPCR ligand, an inhibitor of an intracellular enzyme or a substrate or inhibitor of a drug transporter;

L is selected from a single or double bond, -O-, -S-, amine, COO-, amide, -NN-hydrazine; and saturated or unsaturated, substituted or unsubstituted C₁₋₆₀₀ branched or straight chain aliphatic, aromatic, alicyclic and combinations thereof, any of which may comprise one or more heteroatoms selected from N, O, S, P, wherein optional substituents are selected from any C₁₋₂₀ aliphatic, aromatic or alicyclic substituents any of which may comprise one or more heteroatoms as hereinbefore defined, hydroxy, thiol, halo, amine, hydrazine, oxo, cyano and carbonyl and combinations thereof, and L may be monomeric, oligomeric having oligomeric repeat of 2 to 30 or polymeric having polymeric repeat in excess of 30 up to 300;

m are each independently selected from a whole number integer from 1 to 3;

p is 0 to 3

wherein -Tag is a fluorophore entity -Fl, whereby the compound is of formula I'

(LigJ_L)_m L (J_T Fl)_m (J_T L (J_L Lig)_m)_p

LigJ_L-L-J_T-Fl as defined in claim 47

wherein any optically active fluorescent ligand is present as a racemate or as one of its optically active isomers

wherein Fl is a fluorophore as hereinbefore defined and is selected from the class of dyes in particular including fluorescein, fluorescein derivatives including FITC, and fluorescein-like molecules including Oregon Green™ and its derivatives, Texas red™, 7-nitrobenz-2-oxa-1,3-diazole (NBD) and derivatives thereof, coumarin and derivatives, naphthalene including derivatives of dansyl chloride or its analogues or derivatives, Cascade Blue™, EvoBlue and fluorescent derivatives thereof, pyrenes and pyridyloxazole derivatives, the cyanine dyes, the dyomics (DY dyes and ATTO dyes) and fluorescent derivatives thereof, the Alexafluor dyes and derivatives, BDI dyes including the commercially available Bodipy™ dyes, erythrosin, eosin, pyrenes, anthracenes, acridines, fluorescent phycobiliproteins and their conjugates and fluoresceinated microbeads, Rhodamine and fluorescent derivatives thereof including

RESPONSE TO NOTICE OF NON-COMPLIANT AMENDMENT

Application No.: 10/551,475

Attorney Docket No.: Q111431

Rhodamine Green™ including the tetramethylrhodamines, X-rhodamines and Texas Red derivatives, and Rhodol Green™, coupled to amine groups using the isocyanate, succinimidyl ester or dichlorotriazinyl-reactive groups, and

wherein Lig J_L L J_T is selected from:

xanthine like structures

adenosine like structures;

ethanolamine like structures; and

oxypropanolamine like structures; wherein

linking functionality J_T is amine; and

wherein linker L is selected from branched and straight chain C₁₋₅₀ alkyl, C₆₋₅₀ cycloalkyl or aryl and combinations thereof optionally comprising one or more heteroatoms O and optionally substituted by C₁₋₁₂ aliphatic, or for xanthine like structures L is also selected from a single bond,

with the proviso that when Lig is XAC ie in Lig.a when each of R.a¹ and R.a² is propyl, R.a³ is H and R.a⁴ is -Ph-OCH₂CONH(CH₂)₂NH-, and L is a single bond Fl is not BODIPY™ 630/650 X; or

b) when Lig is ABEA, ie m is 4 and L is a single bond Fl is not BODIPY™ 630/650 X.

69. (withdrawn). A kit comprising a Compound of formula I or I' as hereinbefore defined in Claim 47 associated with information relating to its pharmacological properties in the form of Spectral Properties given as Excitation Max and Emission Max, Fluorescence Lifetime and Emission quantum yield and Pharmacology defined in terms of cells expressing a GPCR receptor as hereinbefore defined or expressing an intracellular cyclic nucleotide phosphodiesterase, or a drug transporter as hereinbefore defined and given as the Inhibition or Antagonism of receptor binding or of receptor functionality together with a value for the Inhibition (pK_B) or Antagonism (pK_I) binding constants, and optionally together with fluorescent images of the pharmacological binding in single living cells illustrating the defined inhibition or antagonism, preferably the pharmacological properties are given as EC₅₀ values for agonist stimulated – or pK_i values for antagonism of agonist stimulated second messenger generation, or substrate K_m values or antagonist K_i values for stimulation or inhibition of intracellular enzymes or drug transporters.

RESPONSE TO NOTICE OF NON-COMPLIANT AMENDMENT

Application No.: 10/551,475

Attorney Docket No.: Q111431

70. (currently amended). Compound of formula IV or IV' or library thereof as hereinbefore defined in Claim 59 ~~useful for linking to any suitable tag of formula V or V'~~ as hereinbefore defined in Claim 59,

~~wherein the linker moiety is of formula~~

~~J-Aq_L-R_L-J''~~

~~wherein each of J and J'' is amine or O, A is CH₂CH₂O, q_L is 1-30 or 31 to 300 and R_L is CH₂CH₂~~

~~or of formula~~

~~J-Aq_L-R_L(A'-J')-J''~~

~~wherein each of J, J' and J'' independently is amine, O or a single bond, q_L is 1, 2 or 3-30 or 31 to 300 and A is CH₂CH₂O or HNCH₂CO or q_L is 1 and A is C(O) or (CH₂)₁₋₈ or q_L is 0, R_L is CH or CH₂CH, q_L is 0 or q_L' is 1 and A' is CH₂ and q_{L''} is 0~~

~~preferably~~

~~O(CH₂CH₂O)_{q_L}CH₂CH₂NH, O(CH₂CH₂O)_{q_L}CH₂CH(CH₂NH)NH,~~

~~OCH(CH₂NH)NH, CH(CH₂NH)NH, C(O)NH, -(CH₂)₁₋₈ or (HNCH₂CO)₁₋₃ (=gly₁₋₃-).~~

71. (withdrawn and currently amended). Fluorophore linker of formula V' or library thereof as hereinbefore defined in Claim 59 ~~wherein the linker moiety is of formula~~

~~J-Aq_L-R_L-J''~~

~~wherein each of J and J'' is amine or O, A is CH₂CH₂O, q_L is 1-30 or 31 to 300 and R_L is CH₂CH₂~~

~~or of formula~~

~~J-Aq_L-R_L(A'-J')-J''~~

~~wherein each of J, J' and J'' independently is amine, O or a single bond, q_L is 1, 2 or 3-30 or 31 to 300 and A is CH₂CH₂O or HNCH₂CO or q_L is 1 and A is C(O) or (CH₂)₁₋₈ or q_L is 0, R_L is CH or CH₂CH, q_L is 0 or q_L' is 1 and A' is CH₂ and q_{L''} is 0~~

~~preferably~~

~~O(CH₂CH₂O)_{q_L}CH₂CH₂NH, O(CH₂CH₂O)_{q_L}CH₂CH(CH₂NH)NH,~~

~~OCH(CH₂NH)NH, CH(CH₂NH)NH, C(O)NH, -(CH₂)₁₋₈ or (HNCH₂CO)₁₋₃ (=gly₁₋₃-).~~

RESPONSE TO NOTICE OF NON-COMPLIANT AMENDMENT

Application No.: 10/551,475

Attorney Docket No.: Q111431

72. (withdrawn and currently amended). Kit comprising ligand precursors, linker precursors and tag precursors of formulae IV, IV', V, V' and/or VI as hereinbefore defined in Claim 59 for preparing a library of compounds of formula I $(\text{Lig} \text{J}_L)_m \text{ L} (\text{J}_T \text{Tag})_m (\text{J}_T \text{L} (\text{J}_L \text{Lig})_m)_p$

and salts thereof wherein any optically active fluorescent ligand is present as a racemate or as one of its optically active isomers

comprising one or a plurality of same or different ligand moieties Lig each linked to one or a plurality of same or different tag moieties Tag via same or different linker moieties L and same or different linking site or linking functionality J_T and J_L

wherein Lig comprises a GPCR ligand, an inhibitor of an intracellular enzyme or a substrate or inhibitor of a drug transporter;

L is selected from a single or double bond, -O-, -S-, amine, COO-, amide, -NN-hydrazine; and saturated or unsaturated, substituted or unsubstituted C₁₋₆₀₀ branched or straight chain aliphatic, aromatic, alicyclic and combinations thereof, any of which may comprise one or more heteroatoms selected from N, O, S, P, wherein optional substituents are selected from any C₁₋₂₀ aliphatic, aromatic or alicyclic substituents any of which may comprise one or more heteroatoms as hereinbefore defined, hydroxy, thiol, halo, amine, hydrazine, oxo, cyano and carbonyl and combinations thereof, and L may be monomeric, oligomeric having oligomeric repeat of 2 to 30 or polymeric having polymeric repeat in excess of 30 up to 300;

Tag is any tagging substrate;

m are each independently selected from a whole number integer from 1 to 3;

p is 0 to 3

wherein one or more of each -Tag in one or more or each library compound is a fluorophore entity -Fl, whereby the library comprises compounds of which one or more or all of which compounds are of formula I'

$(\text{Lig} \text{J}_L)_m \text{ L} (\text{J}_T \text{Fl})_m (\text{J}_T \text{L} (\text{J}_L \text{Lig})_m)_p$

~~characterised in that wherein~~ linking is at same or different linking sites in compounds comprising different Lig, J_L , L J_T and/or - Tag and is at different linking sites in compounds comprising same Lig, J_L , L J_T and/or - Tag

RESPONSE TO NOTICE OF NON-COMPLIANT AMENDMENT

Application No.: 10/551,475

Attorney Docket No.: Q111431

~~with the proviso that when Lig is CGP12177 and L is 1,1,4,4 tetramethyl butylamine C(CH₃)₂(CH₂)₂C(CH₃)₂NH, Fl is not BODIPY® FL, or when L is C(CH₃)₂(CH₂)₂C(CH₃)₂NHCSNH then Fl is not FITC, eosin or erythrosin wherein the or each Fl is selected from a red, near ir or blue dye.~~

73. (withdrawn and currently amended). A library of fluorescent ligands of formula I or I' or a kit comprising a compound thereof as hereinbefore defined in Claim 47 for visualising receptors or receptor binding, assessing pharmacological properties of the fluorescent ligand, in high throughput screening of novel chemical entities that bind to the target receptor, in inhibiting an intracellular enzyme or inhibiting a drug transporter or a substrate of a drug transporter, in studying drug transport or drugs suitable for transport or in distinguishing healthy or diseased tissue.

74. (withdrawn and currently amended). A library of fluorescent ligands of formula I or I' or a kit comprising a compound thereof as hereinbefore defined in claim 47 or 64 for use in a method for receptor binding or inhibition, intracellular enzyme inhibition or drug transport or inhibition and visualisation comprising contacting ~~ta-he~~ library or a compound thereof as defined in claim 47 with a sample comprising live cell material comprising GPCRs, intracellular enzymes or drug transporters in manner to facilitate binding or inhibition thereof or transport thereby, and detecting changes in fluorescence or location thereof.

75. (withdrawn and currently amended). A library of fluorescent ligands of formula I or I' or a kit comprising a compound thereof for use as claimed in claim 74 wherein the library or compound thereof is a fluorescent ligand(s) which has affinity such that it binds ~~permanently~~, semi-permanently or transiently and remains bound when unbound ligand is washed away.

76. (withdrawn and currently amended). A library of fluorescent ligands of formula I or I' or a kit comprising a compound thereof for use as claimed in claim 74 wherein detecting a change in fluorescence is by means of confocal microscopy or fluorescence correlation spectroscopy.

RESPONSE TO NOTICE OF NON-COMPLIANT AMENDMENT

Application No.: 10/551,475

Attorney Docket No.: Q111431

77. (withdrawn and currently amended). A library of fluorescent ligands of formula I or I' or a ~~kit comprising a compound thereof for use as claimed in claim 74 wherein the library or compound thereof comprises fluorescent ligand agonist(s) which maintains its binding affinity and functional activity or is an antagonist which maintains its binding affinity on linking or when linked to fluorescent moiety Fl.~~

78. (withdrawn and currently amended). A kit comprising a library or a compound of formula I or I' as claimed in claim 47 or 64 and a target therefor provided as cell derived material selected from a cell line, expressing a GPCR, intracellular enzyme or drug transporter, membrane containing these proteins derived from such a cell line, solubilised receptor, enzyme or drug transporter or GPCR array from that cell line.

79. (withdrawn). Kit as claimed in Claim 78 wherein the cell derived material is provided in one of three forms: (1) from cells expressing a green fluorescent protein tagged receptor, intracellular enzyme or drug transporter; (2) from cells expressing an epitope tag for a commercially available fluorescent antibody or (3) a wild-type protein for which a specific fluorescent antibody is also provided.

80-82. (canceled).

83. (withdrawn and currently amended). Library as claimed in Claim 59-55 comprising a plurality of compounds of the formula

Lig J_b-L J_f-Fl

wherein any optically active fluorescent ligand is present as a racemate or as one of its optically active isomers

wherein Fl is selected from dyes in particular including fluorescein, fluorescein derivatives including FITC, and fluorescein-like molecules including Oregon Green™ and its derivatives, Texas red™, 7-nitrobenz-2-oxa-1,3-diazole (NBD) and derivatives thereof, coumarin and derivatives, naphthalene including derivatives of dansyl chloride or its analogues or derivatives, Cascade Blue™, EveBlue and fluorescent derivatives thereof, pyrenes and pyridyloxazole derivatives, the cyanine dyes, the dyomics (DY dyes and ATTO dyes) and fluorescent derivatives thereof, the Alexafluor dyes and derivatives, BDI dyes including the commercially available Bodipy™ dyes, erythrosin, eosin, pyrenes, anthracenes, acridines, fluorescent

RESPONSE TO NOTICE OF NON-COMPLIANT AMENDMENT

Application No.: 10/551,475

Attorney Docket No.: Q111431

~~phycoobiliproteins and their conjugates and fluoresceinated microbeads, Rhodamine and fluorescent derivatives thereof including Rhodamine Green™ including the tetramethylrhodamines, X-rhodamines and Texas Red derivatives, and Rhodol Green™, coupled to amine groups using the isoeyanate, succinimidyl ester or dichlorotriazinyl reactive groups, and~~

~~wherein Lig J_L-L-J_T is selected from the formulae Lig.a, Lig.b, Lig.c and Lig.d wherein:~~

Lig.a comprises linking functionality J_L which is amine, and is of the formula, in either of the following forms given:

Lig.a^{1m}



wherein R.a⁴ comprises linking functionality J_L and J_T which is amine;

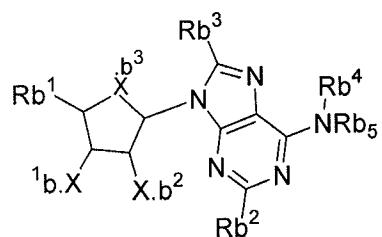
X¹ and X² are each O;

R.a³ is H;

each of R.a¹ and R.a² is n-propyl;

R.a⁴ is p- substituted phenyl wherein the substituent is heteroalkyl amide amine; and includes L which is a single bond or is C₁₋₅₀ alkyl optionally substituted by C₁ alkyl and including the formula -(CH₂)_n where n is 3 to 8, optionally including one or more heteroatoms -O;

Lig.b comprises linking functionality J_L which is amine, and is



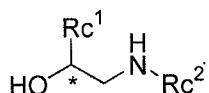
RESPONSE TO NOTICE OF NON-COMPLIANT AMENDMENT

Application No.: 10/551,475

Attorney Docket No.: Q111431

wherein ring substituents X.b¹ and X.b² are each OH;
 ring heteroatom X.b³ is -O- ;
 Rb¹ is CONHET or CH₂OH;
 and each of R.b² and R.b³ is H;
 Rb⁴ is H;
 Rb⁵ comprises linking functionality J_T which is amino, and linker L.b selected from saturated C₁₋₁₂ aliphatic and C₆₋₂₄ aromatic, optionally substituted by one or more C₁ alkyl and optionally including one or more heteroatoms O or cyclic groups;

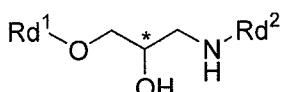
Lig.c comprises linking functionality J_L which is amine and is



as a racemate or as one of its optically active isomers wherein * indicates an optically active centre,

Rc¹ is m-, p- dihydroxyphenyl; and
 Rc² comprises linking functionality J_T which is amine, and linker L.c which is selected from C₁₋₁₂ straight chain alkyl, C₆₋₁₂ cycloalkyl or aryl and combinations thereof optionally comprising one or more heteroatoms O and optionally substituted by C₁ aliphatic;

or Lig.d comprises a linking functionality J_L which is amine and is

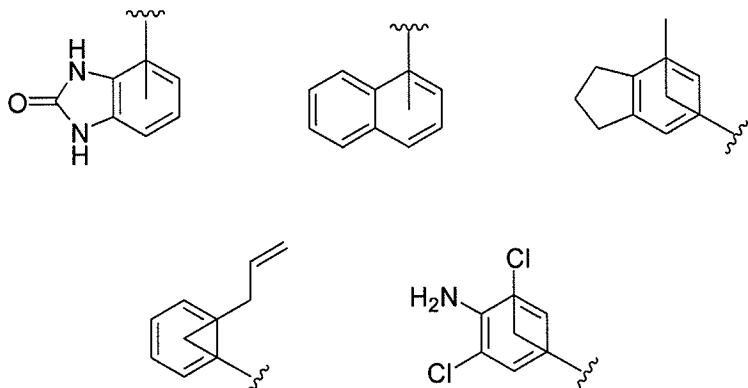


RESPONSE TO NOTICE OF NON-COMPLIANT AMENDMENT

Application No.: 10/551,475

Attorney Docket No.: Q111431

as a racemate or as one of its optically active isomers wherein * indicates an optically active centre,



Rd¹ is selected from the structures

and a substituted C₁₋₂₀ spiro aromatic ring system comprising a single aromatic ring and a heteroaryl and optionally halo substituted; and

Rd² comprises linking functionality J_T which is amine, and linker L.d which is selected from C₁₋₁₂ straight chain alkyl, C₆₋₁₂ cycloalkyl or aryl and combinations thereof optionally comprising one or more heteroatoms O and optionally substituted by C₁ aliphatic; or Rd² is C₁₋₆ straight chain alkyl including ether O and substituted by C₆₋₁₀ aryl which is OH and oxo substituted and comprises linker L.d as hereinbefore defined.

84. (withdrawn). Library as claimed in claim 83 wherein

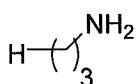
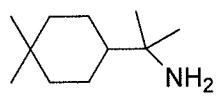
R.a⁴, R.b⁵ or R.c² or R.d² comprises linking functionality J_T which is amino, and linker L.a, L.b, L.c or L.d selected from (CH₂)_m wherein m is 3, 4, 6 or 8 or is in the range 3 to 8 or 2 to 12 optionally including one or more substituents C₁, or J_L L J_T is mono or polyethylene glycol diamine, or L.a is a single bond; or

R.c² or R.d² comprises linking functionality J_T which is amino, and linker L.c or L.d selected from C(CH₃)₂CH₂Ph and mono amino menthane or the structure

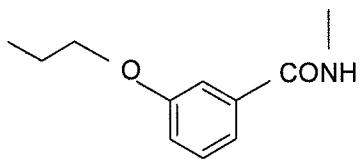
RESPONSE TO NOTICE OF NON-COMPLIANT AMENDMENT

Application No.: 10/551,475

Attorney Docket No.: Q111431



or Rd² comprises the following OH substituted aryl structure wherein linking functionality J_L is shown as amine, Ld is as hereinabove defined and includes J_T which is amine:



85. (canceled).

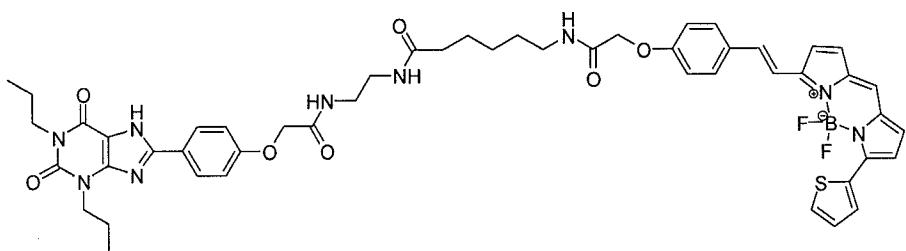
86. (withdrawn and currently amended). Library as claimed in Claim ~~83-47~~ wherein F1 is selected from Texas Red™, Cy5.5 or Cy5 or analogues thereof, DY-630, DY-640, DY-650 or DY-655 or analogues thereof, ATTO 655 or ATTO 680 or analogues thereof, EvoBlue 30 or analogues thereof, Alexa 647 or analogues thereof, BODIPY 630/650 X and analogues thereof including BODIPY 630/650 X.

87. (withdrawn and currently amended). Library as claimed in claim ~~86~~ comprising a compound selected from the following structures wherein any optically active fluorescent ligand is present as a racemate or as one of its optically active isomers:

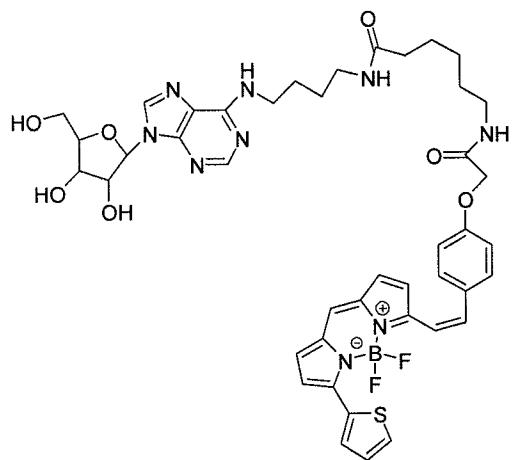
RESPONSE TO NOTICE OF NON-COMPLIANT AMENDMENT

Application No.: 10/551,475

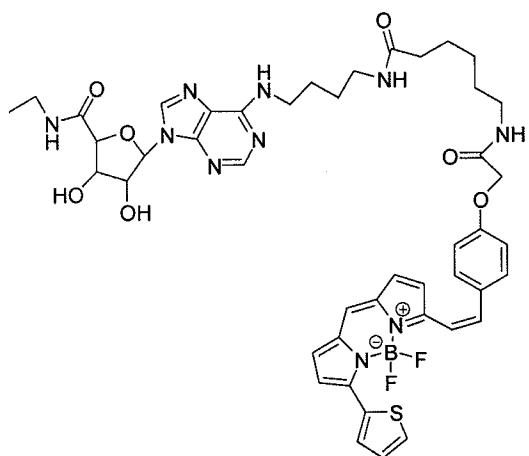
Attorney Docket No.: Q111431



XAC – BODIPY 630/650 X



ABA-BY630

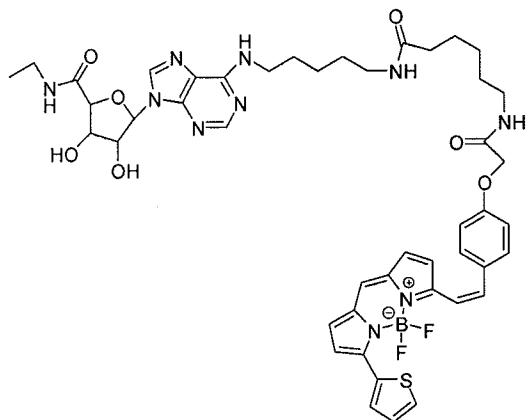


ABEA-BY630

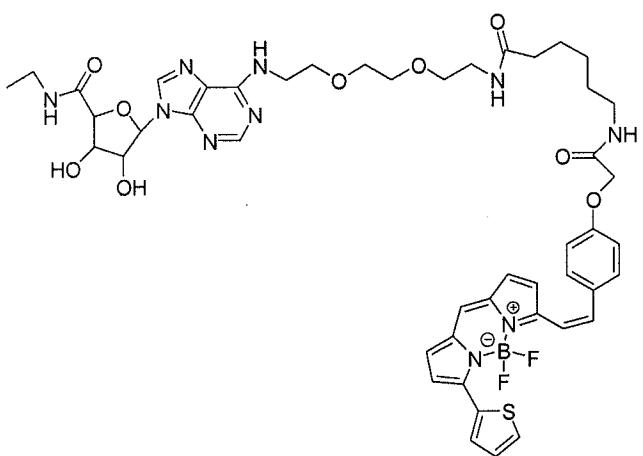
RESPONSE TO NOTICE OF NON-COMPLIANT AMENDMENT

Application No.: 10/551,475

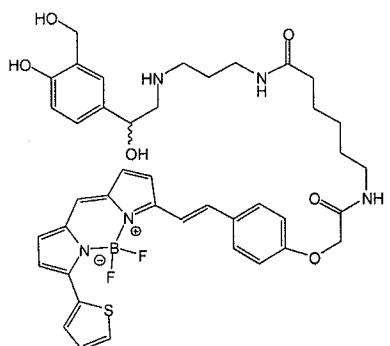
Attorney Docket No.: Q111431



APEA-BY 630



ABIPEA – BY630

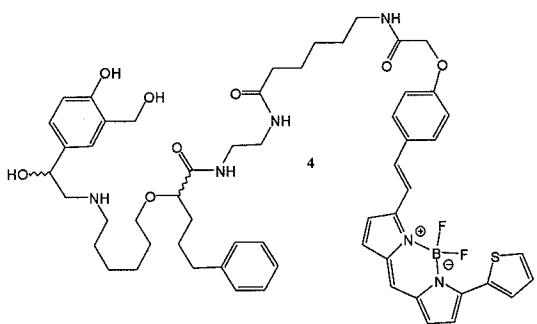


RESPONSE TO NOTICE OF NON-COMPLIANT AMENDMENT

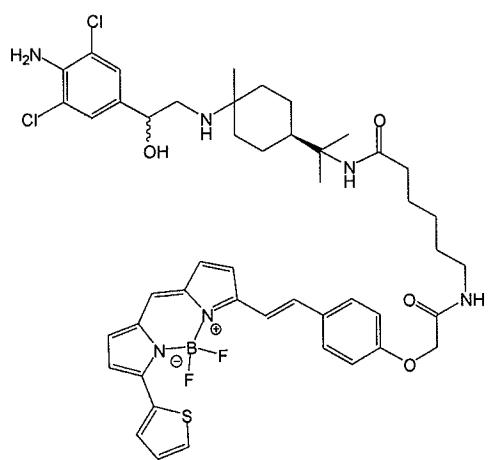
Application No.: 10/551,475

Attorney Docket No.: Q111431

and



Salmeterol BY 630/650

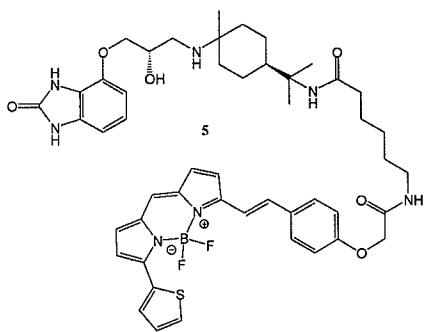


RESPONSE TO NOTICE OF NON-COMPLIANT AMENDMENT

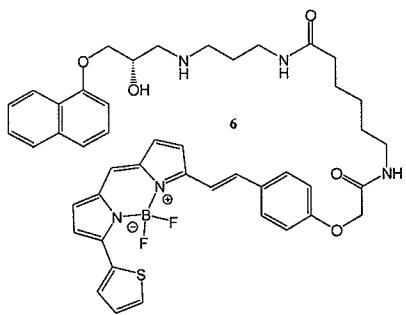
Application No.: 10/551,475

Attorney Docket No.: Q111431

Clenbuterol BY 630/650



CGP12177-BY 630/650

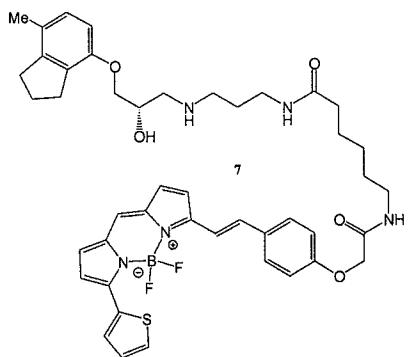


RESPONSE TO NOTICE OF NON-COMPLIANT AMENDMENT

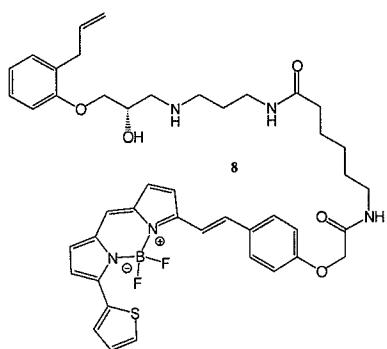
Application No.: 10/551,475

Attorney Docket No.: Q111431

Propranolol BY630/650



ICI118551-BY630/650



Alprenolol-BY630/650

88. (currently amended). Compound as claimed in Claim 67 of the formula

RESPONSE TO NOTICE OF NON-COMPLIANT AMENDMENT

Application No.: 10/551,475

Attorney Docket No.: Q111431

Lig.J_L-L J_T-Fl

wherein any optically active fluorescent ligand is present as a racemate or as one of its optically active isomers

wherein Fl is selected from wherein Fl is selected from dyes in particular including fluorescein, fluorescein derivatives including FITC, and fluorescein like molecules including Oregon Green™ and its derivatives, Texas red™, 7-nitrobenz-2-oxa-1,3-diazole (NBD) and derivatives thereof, coumarin and derivatives, naphthalene including derivatives of dansyl chloride or its analogues or derivatives, Cascade Blue™, EVOBlue and fluorescent derivatives thereof, pyrenes and pyridyloxazole derivatives, the cyanine dyes, the dyomics (DY dyes and ATTO dyes) and fluorescent derivatives thereof, the Alexafluor dyes and derivatives, BDI dyes including the commercially available Bodipy™ dyes, erythrosin, eosin, pyrenes, anthracenes, acridines, fluorescent phycobiliproteins and their conjugates and fluoresceinated microbeads, Rhodamine and fluorescent derivatives thereof including Rhodamine Green™ including the tetramethylrhodamines, X rhodamines and Texas Red derivatives, and Rhodol Green™, coupled to amine groups using the isocyanate, succinimidyl ester or dichlorotriazinyl reactive groups; and

wherein Lig J_L-L J_T is selected from the formulae Lig.a, Lig.b, Lig.c and Lig.d wherein:

Lig.a comprises linking functionality J_L which is amine, and is of the formula, in either of the following forms given:

Lig.a^{1m}

wherein Ra⁴ comprises linking functionality J_L and J_T which is amine;
 X¹ and X² are each O;
 R.a³ is H;

RESPONSE TO NOTICE OF NON-COMPLIANT AMENDMENT

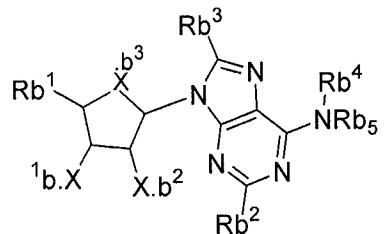
Application No.: 10/551,475

Attorney Docket No.: Q111431

each of R.a¹ and R.a² is n-propyl;

R.a⁴ is p- substituted phenyl wherein the substituent is heteroalkyl amide amine; and includes L which is a single bond or is C₁₋₅₀ alkyl optionally substituted by C₁ alkyl and including the formula -(CH₂)_n where n is 3 to 8, optionally including one or more heteroatoms -O;

Lig.b comprises linking functionality J_L which is amine, and is



wherein ring substituents X.b¹ and X.b² are each OH;

ring heteroatom X.b³ is -O- ;

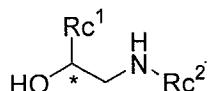
Rb¹ is CONHET or CH₂OH;

and each of R.b² and R.b³ is H;

Rb⁴ is H;

Rb⁵ comprises linking functionality J_T which is amino, and linker L.b selected from saturated C₁₋₁₂ aliphatic and C₆₋₂₄ aromatic, optionally substituted by one or more C₁ alkyl and optionally including one or more heteroatoms O or cyclic groups;

Lig.c comprises linking functionality J_L which is amine and is



as a racemate or as one of its optically active isomers wherein * indicates an optically active centre,

Rc¹ is m-, p- dihydroxyphenyl; and

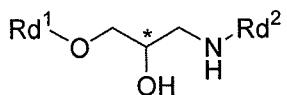
Rc² comprises linking functionality J_T which is amine, and linker L.c which is selected from C₁₋₁₂ straight chain alkyl, C₆₋₁₂ cycloalkyl or aryl and combinations thereof optionally comprising one or more heteroatoms O and optionally substituted by C₁ aliphatic;

RESPONSE TO NOTICE OF NON-COMPLIANT AMENDMENT

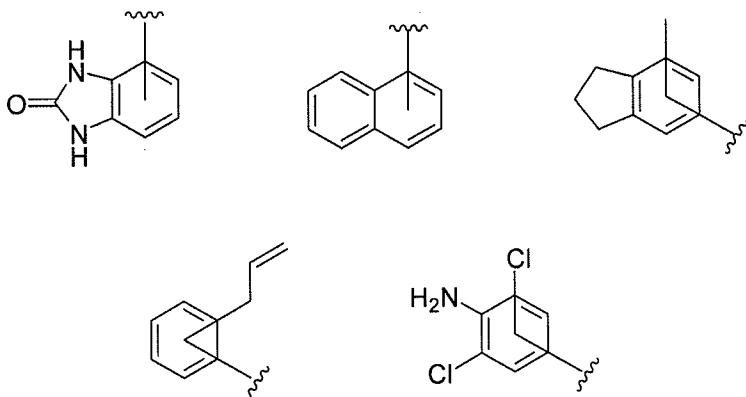
Application No.: 10/551,475

Attorney Docket No.: Q111431

or Lig.d comprises a linking functionality J_L which is amine and is



as a racemate or as one of its optically active isomers wherein * indicates an optically active centre,



Rd^1 is selected from the structures

and a substituted C_{1-20} spiro aromatic ring system comprising a single aromatic ring and a heteroaryl and optionally halo substituted; and

Rd^2 comprises linking functionality J_T which is amine, and linker L.d which is selected from C_{1-12} straight chain alkyl, C_{6-12} cycloalkyl or aryl and combinations thereof optionally comprising one or more heteroatoms O and optionally substituted by C_1 aliphatic; or Rd^2 is C_{1-6} straight chain alkyl including ether O and substituted by C_{6-10} aryl which is OH and oxo substituted and comprises linker L.d as hereinbefore defined,

with the proviso that the compound is not a compound excluded in Claim 18.

89. (currently amended). Compound as claimed in Claim 88 wherein R.a⁴, R.b⁵ or R.c² or R.d² comprises linking functionality J_T which is amino, and linker L.a, L.b, L.c or L.d selected

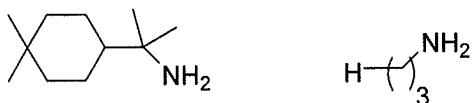
RESPONSE TO NOTICE OF NON-COMPLIANT AMENDMENT

Application No.: 10/551,475

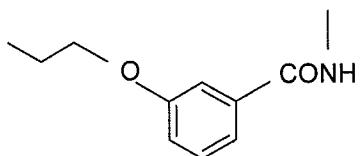
Attorney Docket No.: Q111431

from $(CH_2)_m$ wherein m is 3, 4, 6 or 8 or is in the range 3 to 8 or 2 to 12 optionally including one or more substituents C₁, or J_L L J_T is mono or polyethylene glycol diamine, or L.a is a single bond; or

R.c² or R.d² comprises linking functionality J_T which is amino, and linker L.c or L.d selected from C(CH₃)₂CH₂Ph and mono amino methane or the structure



or R_d² comprises the following OH substituted aryl structure wherein linking functionality J_L is shown as amine, Ld is as hereinabove defined and includes J_T which is amine:



with the proviso that when Liz-Lig is XAC ie in Lig.a when each of R.a¹ and R.a² is propyl, R.a³ is H and R.a⁴ is -Ph-OCH₂CONH(CH₂)₂NH-, and L is a single bond Fl is not BODIPY™ 630/650 X; or

b) when Lig is ABEA, ie m is 4 and L is a single bond Fl is not BODIPY™ 630/650 X.

90. (canceled)

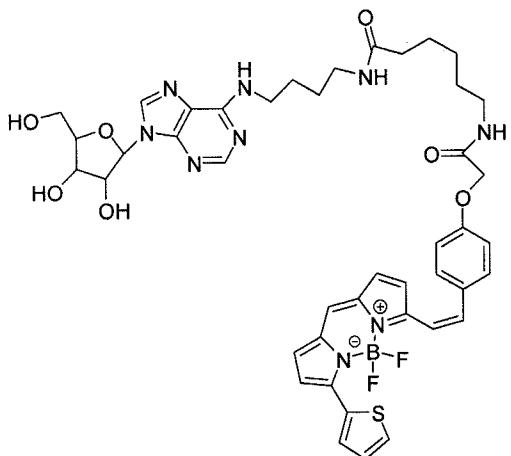
91. (currently amended). Compound as claimed in Claim 88-64 wherein Fl is selected from Texas Red™, Cy5.5 or Cy5 or analogues thereof, DY-630, DY-640, DY-650 or DY-655 or analogues thereof, ATTO 655 or ATTO 680 or analogues thereof, EvoBlue 30 or analogues thereof, Alexa 647 or analogues thereof, BODIPY 630/650-X and analogues thereof including BODIPY 630/650-X.

RESPONSE TO NOTICE OF NON-COMPLIANT AMENDMENT

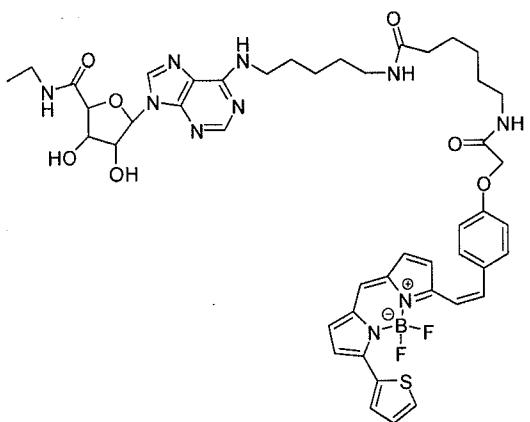
Application No.: 10/551,475

Attorney Docket No.: Q111431

92. (withdrawn and currently amended). Compound selected from the structures wherein any optically active fluorescent ligand is present as a racemate or as one of its optically active isomers:



ABA-BY630

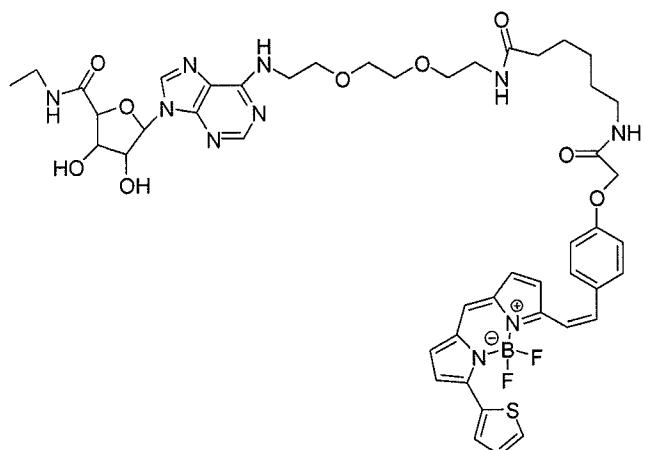


APEA-BY 630

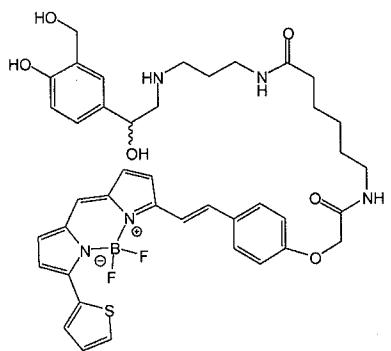
RESPONSE TO NOTICE OF NON-COMPLIANT AMENDMENT

Application No.: 10/551,475

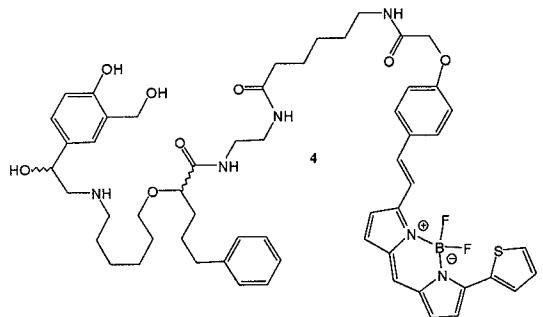
Attorney Docket No.: Q111431



ABIPEA - BY630



And Salmeterol derivative - BY 630/650

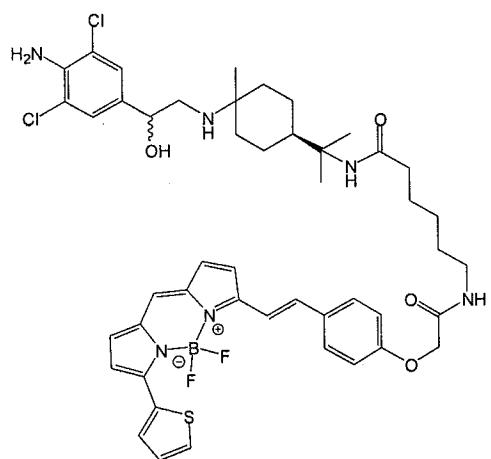


RESPONSE TO NOTICE OF NON-COMPLIANT AMENDMENT

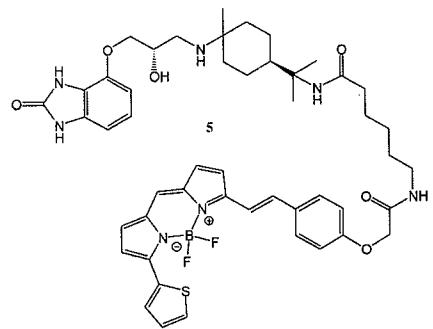
Application No.: 10/551,475

Attorney Docket No.: Q111431

Salmeterol BY 630/650



Clenbuterol BY 630/650

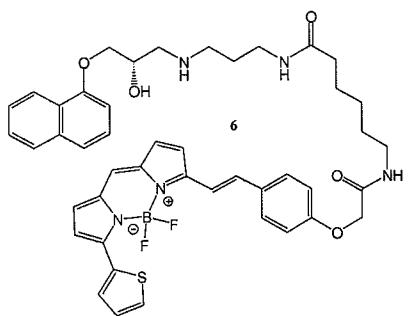


RESPONSE TO NOTICE OF NON-COMPLIANT AMENDMENT

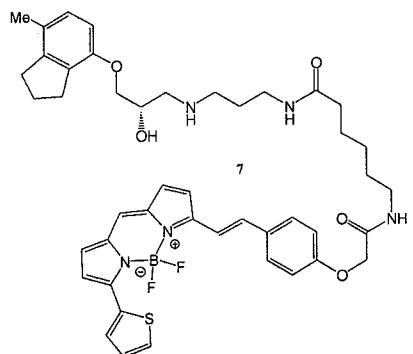
Application No.: 10/551,475

Attorney Docket No.: Q111431

CGP12177-BY 630/650



Propranolol BY630/650

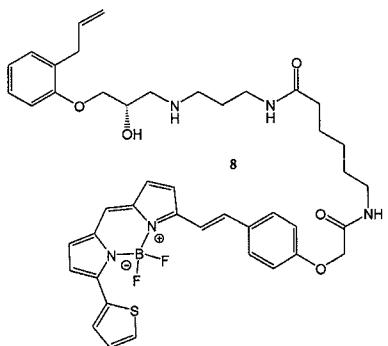


RESPONSE TO NOTICE OF NON-COMPLIANT AMENDMENT

Application No.: 10/551,475

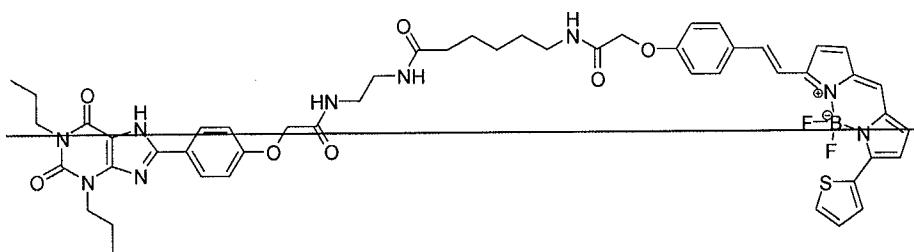
Attorney Docket No.: Q111431

ICI118551-BY630/650



Alprenolol-BY630/650

and optionally additionally



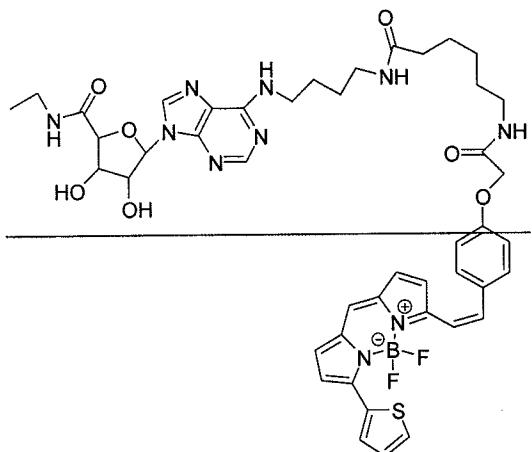
XAC-BODIPY 630/650-X

or

RESPONSE TO NOTICE OF NON-COMPLIANT AMENDMENT

Application No.: 10/551,475

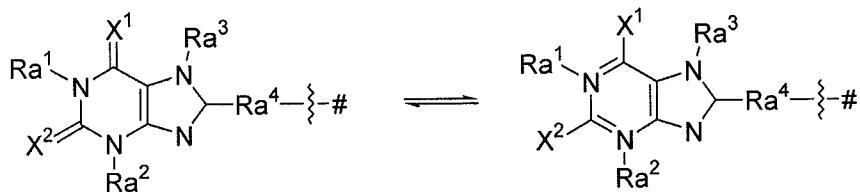
Attorney Docket No.: Q111431



ABEA-BY630.

93. (new and withdrawn). Library of tagged non-peptide ligands comprising moiety Lig and L selected from formula Lig.a-L.a- - Lig.e-L.e associated with a Tag which is an entity -Fl wherein the or each -Fl is selected from a red, near ir or blue dye and wherein:
Lig.a- is suitably of the formula, in either of the following forms given:

Lig.a¹-



Wherein X¹ and X² are each independently selected from H, =O, OR.a, NR.a, NHR.a;
X¹ and X² are each preferably =O;
each of R.a, R.a¹, R.a² and R.a³ independently is selected from H or C₁₋₄ linear or branched alkyl, preferably H, methyl, ethyl, n-propyl, isopropyl, n-butyl, t-butyl or isobutyl optionally mono or multi hydroxy or halo substituted, such as CH₂OH, CH₂F or CH₂CHOHCH₂OH;

RESPONSE TO NOTICE OF NON-COMPLIANT AMENDMENT

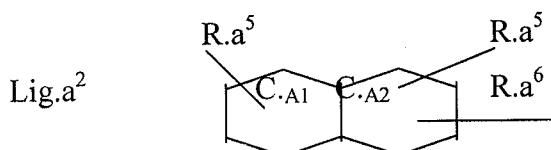
Application No.: 10/551,475

Attorney Docket No.: Q111431

R.a⁴ is selected from a heteroatom O, S or substituted or unsubstituted amine or saturated or unsaturated, substituted or unsubstituted C₁₋₂₀ branched or straight chain aliphatic, aromatic, alicyclic and combinations thereof, any of which may comprise one or more heteroatoms selected from N, O, S, P; wherein optional substituents are selected from any C₁₋₁₂ aliphatic, aromatic or alicyclic substituents any of which may comprise one or more heteroatoms as hereinbefore defined, hydroxy, thiol, halo, amine, hydrazine, oxo, cyano, and the like;

preferably R.a⁴ is selected from optionally substituted aryl, cycloalkyl, alkyl, ketone, (di)amine, (di)amide, more preferably optionally substituted alkoxy, cycloalkyl, amine, amide, carboxylic acid or optionally o-, m- or p- substituted phenyl wherein substituents include aryl, alkyl, cycloalkyl, heteroaryl or heteroalkyl, amine, amide, carboxyl, carbonyl etc, for example is cyclohexyl, cyclopentyl, ethoxy, (CH₂)₂PhPh, CH₂Ph, CONH(CH₂)_nCONH, CH₂CONH(CH₂)₂NH, CH₂PhNHCOCH₂, CH₂CH₂OCOCH₂, succinimidyl ester, NHCOCH₂, CH₂(CH₃)NCOCH₂, H₂N(CH₂)₂NHCOCH₂, H₂N(CH₂)₈NHCOCH₂, H₂NNHCOCH₂, CH₂CONH(CH₂)₂NHCOCH₂, HOPhCH₂N(CH₂CH₃.HOAc)(CH₂)₂NHCOCH₂, heterocyclic-(CH₂)₄CONH(CH₂)₂NHCOCH₂, heterocyclic-NHCON(heterocyclic)COCH₂ and the like;

or Lig.a- is of the formula Lig.a²-



wherein each of C._{A1} and C._{A2} is independently selected from aryl, heteroaryl, cycloalkyl and heterocyclic, more preferably from phenyl, or aryl containing 1 or 2 ring heteroatoms, or heterocyclic containing 1 ring heteroatom and/or 1 ring -C=C- group;

Each of up to seven R.a⁵ is a substituent of a ring carbon or a ring heteroatom and:

RESPONSE TO NOTICE OF NON-COMPLIANT AMENDMENT

Application No.: 10/551,475

Attorney Docket No.: Q111431

is independently selected from H, halo, hydroxy, thiol, amine, COOH, hydrazine, cyano, saturated or unsaturated, substituted or unsubstituted C₁₋₂₀ branched or straight chain aliphatic, aromatic, alicyclic and combinations thereof, any of which may comprise one or more heteroatoms selected from N, O, S, P, and wherein optional substituents are selected from any C₁₋₁₂ aliphatic, aromatic or alicyclic substituents any of which may comprise one or more heteroatoms as hereinbefore defined, hydroxy, thiol, halo, amine, hydrazine, oxo, cyano, and the like, such as =O, OCH₃, CH₂Ph(OCH₃)₂, O(CH₂)₃CON(CH₃)₂.hex, N(CH₂CH₂OH)₂, c.hex, COOCH₂CH₃, CH₂CH₃;

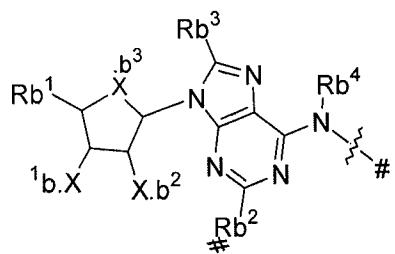
or any two or more of R.a⁵ form a one, two or three ring fused cyclic structure, preferably comprising a fused 3 ring aryl, 5-heterocyclic, 6-heterocyclic structure having 4 ring atoms common with the fused bicyclic Lig.a² structure;

and R.a⁶ is a moiety as defined for R.a⁵ above;

and -L.a- is as hereinbefore defined for -L- and is suitably of formula -L.I- or -L.II- as hereinbefore defined, more preferably is selected from a single bond, amino acid or amide such as a peptide or polypeptide for example gly or gly₃, alkyl of formula -(CH₂)_n where n is 3 to 8, preferably 3, 4 or 6, optionally including one or more heteroatoms or unsaturated groups, such as -O- or -S- or -CH=CH- and the like:

Lig.b is suitably of the formula Lig.b

Lig.b



RESPONSE TO NOTICE OF NON-COMPLIANT AMENDMENT

Application No.: 10/551,475

Attorney Docket No.: Q111431

wherein ring substituents X.b¹ and X.b² are independently selected from hydrocarbon such as alkyl or SR_X, NR_{X.2} and OR_X wherein (each) R_X is selected from H, C₁₋₅alkyl, alkenyl;

ring heteroatom X.b³ is selected from -S-, -O- and -CH₂-;

Rb¹ is selected from saturated or unsaturated, substituted or unsubstituted C₁₋₄ aliphatic, or C₁₋₃ alicyclic optionally including one or more heteroatoms N, O, S, P, wherein substituent(s) are selected from one or more cycloalkyl, heterocyclic, hydroxy, oxo, halo, amine; preferably R.b¹ comprises a carbonyl substituted by H, alkyl or a linear or cyclic primary, secondary or tertiary amine, substituted C₁₋₃ alkyl, cycloalkyl or amide, more preferably cyclopropyl, or CONHC₁₋₃alkyl such as CONHET or CH₂OH

and each of R.b² and R.b³ is selected from H, halo, hydroxy, thiol, amine, COOH, CHO, hydrazine, cyano or saturated or unsaturated, substituted or unsubstituted C₁₋₂₀ branched or straight chain aliphatic, aromatic, alicyclic and combinations thereof, any of which may comprise one or more heteroatoms selected from N, O, S, P; wherein optional substituents are selected from any C₁₋₁₂ aliphatic, aromatic or alicyclic substituents any of which may comprise one or more heteroatoms as hereinbefore defined, hydroxy, thiol, halo, amine, hydrazine, oxo, cyano, and the like, preferably from H, halo or hydroxy, preferably H or Cl;

Rb⁴ is H;

-L.b- is as hereinbefore defined for -L-, more preferably saturated and unsaturated substituted or unsubstituted C₁₋₁₂ aliphatic or C₁₋₂₄ aromatic as defined for -L- preferably including one or more heteroatoms O, S or N, cyclic or heterocyclic groups, more preferably is of formula -L.I- or -L.II- as hereinbefore defined, most preferably is -(CH₂)_m wherein m is 2 to 12, preferably 3, 4, 6 or 8, or is -(Ph-CH₂CONH)₂(CH₂)₂-;

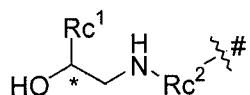
Lig.c is suitably a non-peptide of the formula

Lig.c HOC*(R.c¹)CH₂NH-R.c²-

RESPONSE TO NOTICE OF NON-COMPLIANT AMENDMENT

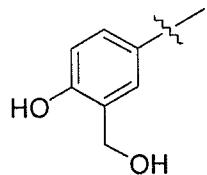
Application No.: 10/551,475

Attorney Docket No.: Q111431



Where * indicates an optically active centre and

Wherein R.c¹ is C₆₋₁₄ aryl optionally including one or more heteroatoms selected from H, O, optionally substituted by OH, Hal eg Cl, NH₂, NHC₁₋₃alkyl, sulphonamide, oxoamine (-CONH₂) and the like, more preferably mono, di or tri substituted phenyl or quinoline wherein substituents include OH, Cl or NH₂, more preferably m-CH₂OH, p-OH phenyl, m-,p-dihydroxy phenol or m-,m-dihydroxyphenol, m-,m-diCl, p-NH₂ phenol, p-OH, m-CONH₂ phenol or 5-OH, 8-quinoline and the like, such as



R.c² is selected from saturated or unsaturated, substituted or unsubstituted C₁₋₂₀, preferably C₁₋₁₂, branched or straight chain aliphatic, aromatic, alicyclic and combinations thereof, any of which may comprise one or more heteroatoms selected from N, O, S, P; wherein optional substituents are selected from any optionally substituted C₁₋₁₂ aliphatic, aromatic or alicyclic substituents any of which may comprise one or more heteroatoms as hereinbefore defined, hydroxy, thiol, halo, amine, hydrazine, oxo, cyano, and the like and combinations thereof;

Preferably R.c² is selected from C₁₋₆ branched or straight chain aliphatic, C₆₋₁₀ araliphatic optionally substituted by OH and optionally including heteroatoms selected from N,O, preferably including an ether O, such as selected from -(CH₂)₆OCH((CH₂)₃Ph), CHCH₃(CH₂)₂Ph, CHCH₃CH₂PhOH, C(CH₃)₂CH₂;

RESPONSE TO NOTICE OF NON-COMPLIANT AMENDMENT

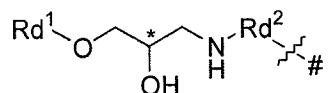
Application No.: 10/551,475

Attorney Docket No.: Q111431

-L.c- is as hereinbefore defined for -L- and is suitably of formula -L.I- or -L.II- as hereinbefore defined, more preferably is selected from C₁₋₁₂ alkyl, amide etc;

Lig.d is suitably a non-peptide of the formula

Lig.d R.d¹ OCH₂C*HOHCH₂NH-R.d²-#



Where * indicates an optically active centre and where # indicates the site of linking to the fluorescent tagging moiety

Wherein R.d¹ is saturated or unsaturated, substituted or unsubstituted C₁₋₂₀ branched or straight chain aliphatic, aromatic, alicyclic and combinations thereof, any of which may comprise one or more heteroatoms selected from N, O, S, P; wherein optional substituents are selected from any C₁₋₁₂ aliphatic, aromatic or alicyclic substituents any of which may comprise one or more heteroatoms as hereinbefore defined, hydroxy, thiol, halo, amine, hydrazine, oxo, cyano, and the like;

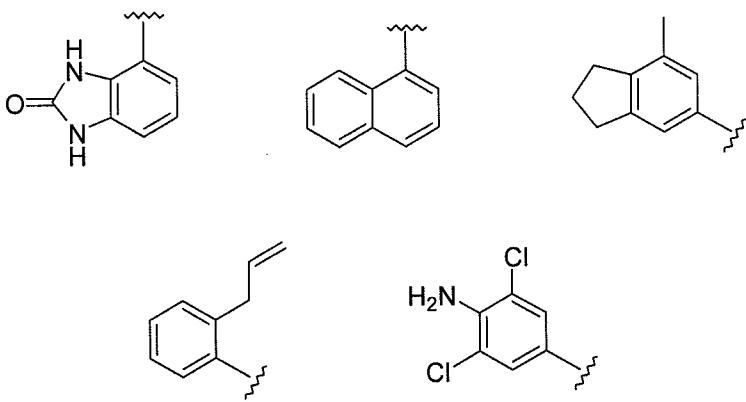
Preferably R.d¹ is substituted or unsubstituted C₁₋₂₄ aralkyl or heteroaralkyl, including single ring and fused ring systems with (hetero)aryl or cycloalkyl rings, wherein optional substituents include C₁₋₆ alkyl, alkoxy, ether, carbonyl, alkenyl, amine, amide each optionally carbonyl, amide, halo or OH substituted, or halo such as chloro or OH, preferably R.d¹ is unsubstituted or substituted alkyl, alkenyl, halo, amine, amide, carbonyl, ketone, ether substituted phenyl or naphthyl, illustrated as follows, most preferably mono-, di-, tri- or tetra substituted mono or polycyclic

RESPONSE TO NOTICE OF NON-COMPLIANT AMENDMENT

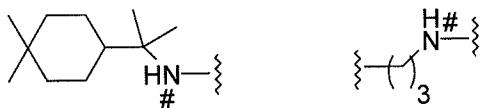
Application No.: 10/551,475

Attorney Docket No.: Q111431

fused aryl or cycloaryl or heterocycloaryl such as phenyl, carbazole or structures shown below or spiro ring systems, most preferably mono-, di-, tri- or tetra alkoxyalkyl, alkoxyalkoxyalkyl or CF₃ substituted phenyl or unsubstituted or monosubstituted naphthalene or 5,6 ring systems most preferably of the structures:



R.d² is substituted or unsubstituted amine, saturated or unsaturated, substituted or unsubstituted C₁₋₁₂ branched or straight chain aliphatic, aromatic, alicyclic and combinations thereof, any of which may comprise one or more heteroatoms selected from N, O, S, P; wherein optional substituents are selected from any C₁₋₁₂ aliphatic, aromatic or alicyclic substituents any of which may comprise one or more heteroatoms as hereinbefore defined, hydroxy, thiol, halo, amine, hydrazine, oxo, cyano, and the like, more preferably amine, C₁₋₆ branched or straight chain alkyl optionally including ether O, and optionally substituted by C₆₋₁₀ aryl, for example of the formula:



i.pr, i.bu, CH₂CH₂O (m-CONH₂, p-OH) phenol, CH₂CH₂O (o-OCH₃) phenol

-L.d- is as hereinbefore defined for -L- and is suitably of formula -L.I- or -L.II- as hereinbefore defined, more preferably is a single bond or is as hereinbefore defined for -L.a-;

RESPONSE TO NOTICE OF NON-COMPLIANT AMENDMENT

Application No.: 10/551,475

Attorney Docket No.: Q111431

Lig.e

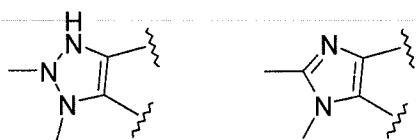
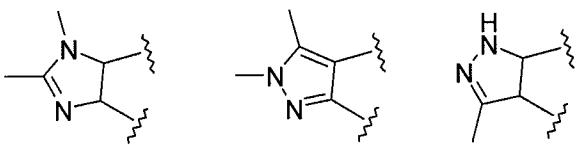
comprises a cell permeant moiety or is associated with a cell permeant L or Fl moiety and is suitably of the formula , in either of the following forms given:

Lig.e¹

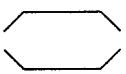


wherein

h is selected from



each optionally substituted by R.e³ – R.e⁴ wherein R.e¹ – R.e⁴ are as R.a¹ – R.a⁴ defined above or in which R.e³ is C₅₋₉linear or branched alkyl, optionally mono or multi hydroxy or halo substituted or is aryl optionally substituted by alkoxy, sulfonyl and the like eg ortho-OEt, meta-SO₂NHCH₃



RESPONSE TO NOTICE OF NON-COMPLIANT AMENDMENT

Application No.: 10/551,475

Attorney Docket No.: Q111431

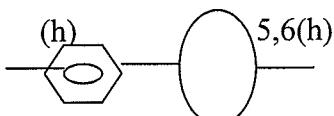
each X is independently selected from H, =O, -OR.e², =N, HN, NR.e⁵, HR.e⁶, and aryl optionally substituted by ether; or X is aryl optionally alkyl or alkoxy substituted such as Ph-ortho-OCH₂CH₂CH₃;

and where R.e⁵ is as defined above for R.e¹ above or forms a fused cyclic ring together with the adjacent ring N atom; preferably 1 or 2 fused 5 membered cyclic rings;

and R.e⁶ is as defined above for R.e¹ above or is selected from optionally substituted phenyl wherein optional substituents include ether such as o-ethoxy or o-propoxy, alkyl, OH and the like, sulphonyl, carbonyl and the like substituted by heterocyclic, or cyclic C₅₋₈ alkyl such as methyl, piperazinyl, sulphonyl and the like;

or Lig.e is of the formula Lig.e²

Lig.e²

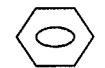


Wherein

each spiro ring optionally comprises zero or one or more heteroatoms h which are preferably N, more preferably or 1 N heteroatom and



(h)



comprises zero

5,6(h) comprises zero, 1 or 2 N

heteroatoms and is unsaturated or comprises one or two -C=C- or -C=N- groups; and wherein each ring is optionally substituted by one or more oxo, CO, COOH, C₁₋₆ alkyl or linear or cyclic alkoxy such as methoxy, ethoxy or cyclopentyloxy optionally substituted by one or more oxo, CO, COOH, CN, or C₁₋₆ alicyclic or amine groups, amine or one or more spiro or fused heterocycles;

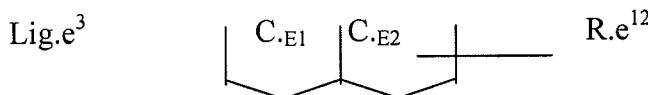
or Lig.e is of the formula Lig.e³



RESPONSE TO NOTICE OF NON-COMPLIANT AMENDMENT

Application No.: 10/551,475

Attorney Docket No.: Q111431



Wherein each of C.E1 and C.E2 is independently selected from aryl, heteroaryl, cyloalkyl and heterocyclic, more preferably from phenyl, or aryl containing 1 or 2 ring heteroatoms, or heterocyclic containing 1 ring heteroatom and/or 1 ring -C=C- group;

Each of up to seven R.e¹¹ is a substituent of a ring carbon or a ring heteroatom and:

is independently selected from saturated or unsaturated, substituted or unsubstituted C₁₋₂₀ branched or straight chain aliphatic, aromatic, alicyclic and combinations thereof, any of which may comprise one or more heteroatoms selected from N, O, S, P, and wherein optional substituents are selected from any C₁₋₁₂ aliphatic, aromatic or alicyclic substituents any of which may comprise one or more heteroatoms as hereinbefore defined, hydroxy, thiol, halo, amine, hydrazine, oxo, cyano, and the like, such as =O, OCH₃, CH₂Ph(OCH₃)₂, O(CH₂)₃CON(CH₃)₂c.hex, N(CH₂CH₂OH)₂, c.hex, COOCH₂CH₃, CH₂CH₃;

or any two or more of R.e¹¹ form a one, two or three ring fused cyclic structure, preferably comprising a fused 3 ring aryl, 5-heterocyclic, 6-heterocyclic structure having 4 ring atoms common with the fused bicyclic Lig.e³ structure;

and R.e¹² is a moiety as defined for R.e¹¹ above;

Preferably Lig.e is of the formula Lig.e¹ as hereinbefore defined in particular where R.e² and R.e³ are respectively propyl and butyl;

-L.e- is suitably as hereinbefore defined for -L.a-.

94. (new and withdrawn). Library as claimed in claim 93 wherein the or each F1 is selected from the following dyes: Texas red™, coumarin and derivatives, Cascade Blue™, EvoBlue and fluorescent derivatives thereof, pyrenes and pyridyloxazole derivatives, the cyanine dyes, the dyomics (DY dyes and ATTO dyes) and fluorescent derivatives thereof, the Alexafluor dyes and derivatives, BDI dyes including the commercially available Bodipy™ dyes, pyrenes,

RESPONSE TO NOTICE OF NON-COMPLIANT AMENDMENT

Application No.: 10/551,475

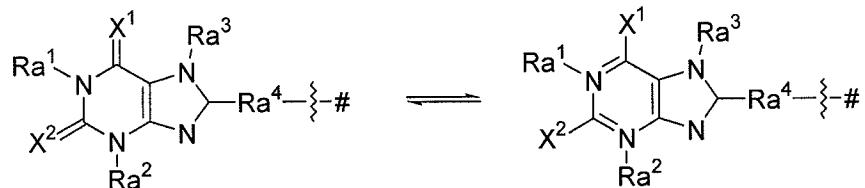
Attorney Docket No.: Q111431

anthracenes, acridines, fluorescent phycobiliproteins and their conjugates and fluoresceinated microbeads, and Texas Red derivatives, coupled to amine groups using the isocyanate, succinimidyl ester or dichlorotriazinyl-reactive groups.

95. (new): Compound which is a tagged non-peptide ligand comprising moiety Lig and L selected from formula Lig.a-L.a- - Lig.e-L.e associated with a Tag which is an entity -Fl wherein -Fl is selected from a red, near ir or blue dye and wherein:

Lig.a- is suitably of the formula, in either of the following forms given:

Lig.a¹-



Wherein X¹ and X² are each independently selected from H, =O, OR.a, NR.a, NHR.a;
 X¹ and X² are each preferably =O;
 each of R.a, R.a¹, R.a² and R.a³ independently is selected from H or C₁₋₄ linear or branched alkyl, preferably H, methyl, ethyl, n-propyl, isopropyl, n-butyl, t-butyl or isobutyl optionally mono or multi hydroxy or halo substituted, such as CH₂OH, CH₂F or CH₂CHOHCH₂OH;
 R.a⁴ is selected from a heteroatom O, S or substituted or unsubstituted amine or saturated or unsaturated, substituted or unsubstituted C₁₋₂₀ branched or straight chain aliphatic, aromatic, alicyclic and combinations thereof, any of which may comprise one or more heteroatoms selected from N, O, S, P; wherein optional substituents are selected from any C₁₋₁₂ aliphatic, aromatic or alicyclic substituents any of which may comprise one or more heteroatoms as hereinbefore defined, hydroxy, thiol, halo, amine, hydrazine, oxo, cyano, and the like;

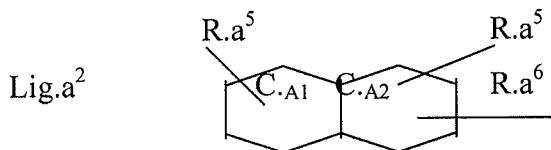
RESPONSE TO NOTICE OF NON-COMPLIANT AMENDMENT

Application No.: 10/551,475

Attorney Docket No.: Q111431

preferably R.a⁴ is selected from optionally substituted aryl, cycloalkyl, alkyl, ketone, (di)amine, (di)amide, more preferably optionally substituted alkoxy, cycloalkyl, amine, amide, carboxylic acid or optionally o-, m- or p- substituted phenyl wherein substituents include aryl, alkyl, cycloalkyl, heteroaryl or heteroalkyl, amine, amide, carboxyl, carbonyl etc, for example is cyclohexyl, cyclopentyl, ethoxy, (CH₂)₂PhPh, CH₂Ph, CONH(CH₂)_nCONH, CH₂CONH(CH₂)₂NH, CH₂PhNHCOCH₂, CH₂CH₂OCOCH₂, succinimidyl ester, NHCOCH₂, CH₂(CH₃)NCOCH₂, H₂N(CH₂)₂NHCOCH₂, H₂N(CH₂)₈NHCOCH₂, H₂NNHCOCH₂, CH₂CONH(CH₂)₂NHCOCH₂, HOPhCH₂N(CH₂CH₃.HOAc)(CH₂)₂NHCOCH₂, heterocyclic-(CH₂)₄CONH(CH₂)₂NHCOCH₂, heterocyclic-NHCON(heterocyclic)COCH₂ and the like;

or Lig.a- is of the formula Lig.a²-



wherein each of C._{A1} and C._{A2} is independently selected from aryl, heteroaryl, cycloalkyl and heterocyclic, more preferably from phenyl, or aryl containing 1 or 2 ring heteroatoms, or heterocyclic containing 1 ring heteroatom and/or 1 ring -C=C- group;

Each of up to seven R.a⁵ is a substituent of a ring carbon or a ring heteroatom and:

is independently selected from H, halo, hydroxy, thiol, amine, COOH, hydrazine, cyano, saturated or unsaturated, substituted or unsubstituted C₁₋₂₀ branched or straight chain aliphatic, aromatic, alicyclic and combinations thereof, any of which may comprise one or more heteroatoms selected from N, O, S, P, and wherein optional substituents are selected from any C₁₋₁₂ aliphatic, aromatic or alicyclic substituents any of which may comprise one or more heteroatoms as hereinbefore defined, hydroxy, thiol, halo, amine,

RESPONSE TO NOTICE OF NON-COMPLIANT AMENDMENT

Application No.: 10/551,475

Attorney Docket No.: Q111431

hydrazine, oxo, cyano, and the like, such as =O, OCH₃, CH₂Ph(OCH₃)₂, O(CH₂)₃CON(CH₃)c.hex, N(CH₂CH₂OH)₂, c.hex, COOCH₂CH₃, CH₂CH₃;

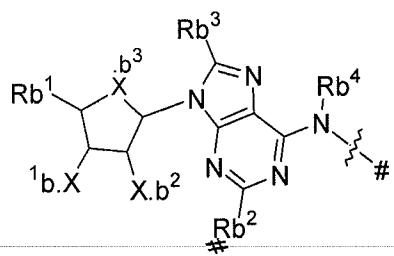
or any two or more of R.a⁵ form a one, two or three ring fused cyclic structure, preferably comprising a fused 3 ring aryl, 5-heterocyclic, 6-heterocyclic structure having 4 ring atoms common with the fused bicyclic Lig.a² structure;

and R.a⁶ is a moiety as defined for R.a⁵ above;

and -L.a- is as hereinbefore defined for -L- and is suitably of formula -L.I- or -L.II- as hereinbefore defined, more preferably is selected from a single bond, amino acid or amide such as a peptide or polypeptide for example gly or gly₃, alkyl of formula -(CH₂)_n where n is 3 to 8, preferably 3, 4 or 6, optionally including one or more heteroatoms or unsaturated groups, such as -O- or -S- or -CH=CH- and the like:

Lig.b is suitably of the formula Lig.b

Lig.b



wherein ring substituents X.b¹ and X.b² are independently selected from hydrocarbon such as alkyl or SR_X, NR_{X.2} and OR_X wherein (each) R_X is selected from H, C₁₋₅alkyl, alkenyl;

ring heteroatom X.b³ is selected from -S-, -O- and -CH₂-;

Rb¹ is selected from saturated or unsaturated, substituted or unsubstituted C₁₋₄ aliphatic, or C₁₋₃ alicyclic optionally including one or more heteroatoms N, O, S, P, wherein substituent(s) are selected from one or more cycloalkyl, heterocyclic,

RESPONSE TO NOTICE OF NON-COMPLIANT AMENDMENT

Application No.: 10/551,475

Attorney Docket No.: Q111431

hydroxy, oxo, halo, amine; preferably R.b¹ comprises a carbonyl substituted by H, alkyl or a linear or cyclic primary, secondary or tertiary amine, substituted C₁₋₃ alkyl, cycloalkyl or amide, more preferably cyclopropyl, or CONHC₁₋₃alkyl such as CONHET or CH₂OH

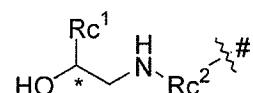
and each of R.b² and R.b³ is selected from H, halo, hydroxy, thiol, amine, COOH, CHO, hydrazine, cyano or saturated or unsaturated, substituted or unsubstituted C₁₋₂₀ branched or straight chain aliphatic, aromatic, alicyclic and combinations thereof, any of which may comprise one or more heteroatoms selected from N, O, S, P; wherein optional substituents are selected from any C₁₋₁₂ aliphatic, aromatic or alicyclic substituents any of which may comprise one or more heteroatoms as hereinbefore defined, hydroxy, thiol, halo, amine, hydrazine, oxo, cyano, and the like, preferably from H, halo or hydroxy, preferably H or Cl;

Rb⁴ is H;

-L.b- is as hereinbefore defined for -L-, more preferably saturated and unsaturated substituted or unsubstituted C₁₋₁₂ aliphatic or C₁₋₂₄ aromatic as defined for -L- preferably including one or more heteroatoms O, S or N, cyclic or heterocyclic groups, more preferably is of formula -L.I- or -L.II- as hereinbefore defined, most preferably is -(CH₂)_m wherein m is 2 to 12, preferably 3, 4, 6 or 8, or is -(Ph-CH₂CONH)₂(CH₂)₂-;

Lig.c is suitably a non-peptide of the formula

Lig.c HO-C*(R.c¹)-CH₂NH-R.c²-



Where * indicates an optically active centre and

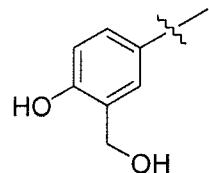
Wherein R.c¹ is C₆₋₁₄ aryl optionally including one or more heteroatoms selected from H, O, optionally substituted by OH, Hal eg Cl, NH₂, NHC₁₋₃alkyl, sulphonamide,

RESPONSE TO NOTICE OF NON-COMPLIANT AMENDMENT

Application No.: 10/551,475

Attorney Docket No.: Q111431

oxoamine (-CONH₂) and the like, more preferably mono, di or tri substituted phenyl or quinoline wherein substituents include OH, Cl or NH₂, more preferably m-CH₂OH, p-OH phenyl, m-,p-dihydroxy phenol or m-,m-dihydroxyphenol, m-,m-diCl, p-NH₂ phenol, p-OH, m-CONH₂ phenol or 5-OH, 8-quinoline and the like, such as



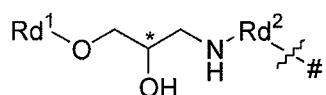
R.c² is selected from saturated or unsaturated, substituted or unsubstituted C₁₋₂₀, preferably C₁₋₁₂, branched or straight chain aliphatic, aromatic, alicyclic and combinations thereof, any of which may comprise one or more heteroatoms selected from N, O, S, P; wherein optional substituents are selected from any optionally substituted C₁₋₁₂ aliphatic, aromatic or alicyclic substituents any of which may comprise one or more heteroatoms as hereinbefore defined, hydroxy, thiol, halo, amine, hydrazine, oxo, cyano, and the like and combinations thereof;

Preferably R.c² is selected from C₁₋₆ branched or straight chain aliphatic, C₆₋₁₀ araliphatic optionally substituted by OH and optionally including heteroatoms selected from N,O, preferably including an ether O, such as selected from -(CH₂)₆OCH((CH₂)₃Ph), CHCH₃(CH₂)₂Ph, CHCH₃CH₂PhOH, C(CH₃)₂CH₂;

-L.c- is as hereinbefore defined for -L- and is suitably of formula -L.I- or -L.II- as hereinbefore defined, more preferably is selected from C₁₋₁₂ alkyl, amide etc;

Lig.d is suitably a non-peptide of the formula

Lig.d R.d¹ OCH₂C*HOHCH₂NH-R.d²#



RESPONSE TO NOTICE OF NON-COMPLIANT AMENDMENT

Application No.: 10/551,475

Attorney Docket No.: Q111431

Where * indicates an optically active centre and where # indicates the site of linking to the fluorescent tagging moiety

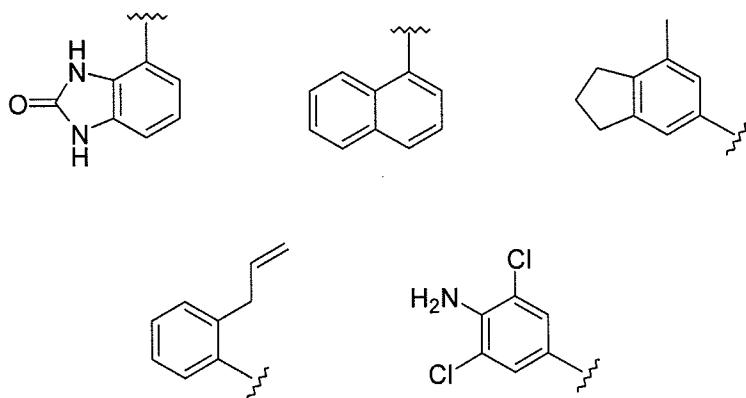
Wherein R.d¹ is saturated or unsaturated, substituted or unsubstituted C₁₋₂₀ branched or straight chain aliphatic, aromatic, alicyclic and combinations thereof, any of which may comprise one or more heteroatoms selected from N, O, S, P; wherein optional substituents are selected from any C₁₋₁₂ aliphatic, aromatic or alicyclic substituents any of which may comprise one or more heteroatoms as hereinbefore defined, hydroxy, thiol, halo, amine, hydrazine, oxo, cyano, and the like;

Preferably R.d¹ is substituted or unsubstituted C₁₋₂₄ aralkyl or heteroaralkyl, including single ring and fused ring systems with (hetero)aryl or cycloalkyl rings, wherein optional substituents include C₁₋₆ alkyl, alkoxy, ether, carbonyl, alkenyl, amine, amide each optionally carbonyl, amide, halo or OH substituted, or halo such as chloro or OH, preferably R.d¹ is unsubstituted or substituted alkyl, alkenyl, halo, amine, amide, carbonyl, ketone, ether substituted phenyl or naphthyl, illustrated as follows, most preferably mono-, di-, tri- or tetra substituted mono or polycyclic fused aryl or cycloaryl or heterocycloaryl such as phenyl, carbazole or structures shown below or spiro ring systems, most preferably mono-, di-, tri- or tetra alkoxyalkyl, alkoxyalkoxyalkyl or CF₃ substituted phenyl or unsubstituted or monosubstituted naphthalene or 5,6 ring systems most preferably of the structures:

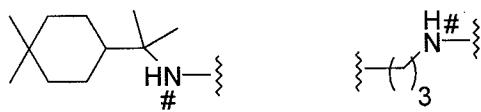
RESPONSE TO NOTICE OF NON-COMPLIANT AMENDMENT

Application No.: 10/551,475

Attorney Docket No.: Q111431



R.d² is substituted or unsubstituted amine, saturated or unsaturated, substituted or unsubstituted C₁₋₁₂ branched or straight chain aliphatic, aromatic, alicyclic and combinations thereof, any of which may comprise one or more heteroatoms selected from N, O, S, P; wherein optional substituents are selected from any C₁₋₁₂ aliphatic, aromatic or alicyclic substituents any of which may comprise one or more heteroatoms as hereinbefore defined, hydroxy, thiol, halo, amine, hydrazine, oxo, cyano, and the like, more preferably amine, C₁₋₆ branched or straight chain alkyl optionally including ether O, and optionally substituted by C₆₋₁₀ aryl, for example of the formula:



i.pr, i.bu, CH₂CH₂O (m-CONH₂, p-OH) phenol, CH₂CH₂O (o-OCH₃) phenol

-L.d- is as hereinbefore defined for -L- and is suitably of formula -L.I- or -L.II- as hereinbefore defined, more preferably is a single bond or is as hereinbefore defined for -L.a-;

Lig.e comprises a cell permeant moiety or is associated with a cell permeant L or F1 moiety and is suitably of the formula , in either of the following forms given:

RESPONSE TO NOTICE OF NON-COMPLIANT AMENDMENT

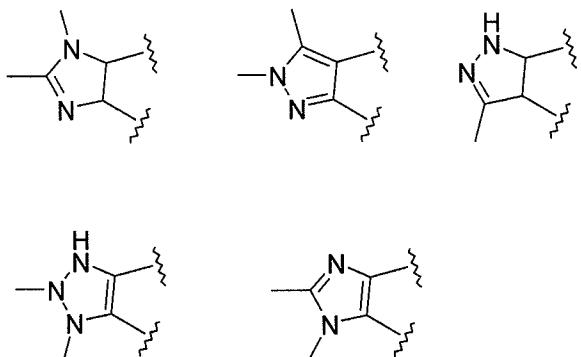
Application No.: 10/551,475

Attorney Docket No.: Q111431

Lig.e¹



wherein h is selected from



each optionally substituted by R.e³ – R.e⁴ wherein R.e¹ – R.e⁴ are as R.a¹ – R.a⁴ defined above or in which R.e³ is C₅₋₉ linear or branched alkyl, optionally mono or multi hydroxy or halo substituted or is aryl optionally substituted by alkoxy, sulfonyl and the like eg ortho-OEt, meta-SO₂N HCH₃
each X is independently selected from H, =O, OR.e², =N, HN, NR.e⁵, HR.e⁶, and aryl optionally substituted by ether; or X is aryl optionally alkyl or alkoxy substituted such as Ph-ortho-OCH₂CH₂CH₃;

RESPONSE TO NOTICE OF NON-COMPLIANT AMENDMENT

Application No.: 10/551,475

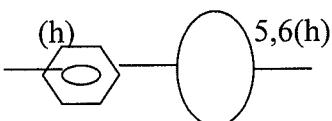
Attorney Docket No.: Q111431

and where R.e⁵ is as defined above for R.e¹ above or forms a fused cyclic ring together with the adjacent ring N atom; preferably 1 or 2 fused 5 membered cyclic rings;

and R.e⁶ is as defined above for R.e¹ above or is selected from optionally substituted phenyl wherein optional substituents include ether such as o-ethoxy or o-propoxy, alkyl, OH and the like, sulphonyl, carbonyl and the like substituted by heterocyclic, or cyclic C₅₋₈ alkyl such as methyl, piperazinyl, sulphonyl and the like;

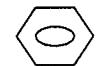
or Lig.e is of the formula Lig.e²

Lig.e²



Wherein

each spiro ring optionally comprises zero or one or more heteroatoms h which are preferably N, more preferably or 1 N heteroatom and

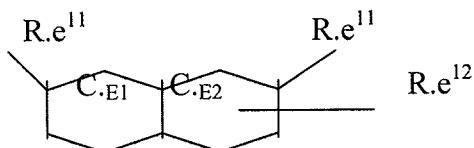


comprises zero
5,6(h) comprises zero, 1 or 2 N

heteroatoms and is unsaturated or comprises one or two -C=C- or -C=N- groups; and wherein each ring is optionally substituted by one or more oxo, CO, COOH, C₁₋₆ alkyl or linear or cyclic alkoxy such as methoxy, ethoxy or cyclopentyloxy optionally substituted by one or more oxo, CO, COOH, CN, or C₁₋₆ alicyclic or amine groups, amine or one or more spiro or fused heterocycles;

or Lig.e is of the formula Lig.e³

Lig.e³



RESPONSE TO NOTICE OF NON-COMPLIANT AMENDMENT

Application No.: 10/551,475

Attorney Docket No.: Q111431

Wherein each of C._{E1} and C._{E2} is independently selected from aryl, heteroaryl, cyloalkyl and heterocyclic, more preferably from phenyl, or aryl containing 1 or 2 ring heteroatoms, or heterocyclic containing 1 ring heteroatom and/or 1 ring -C=C- group;

Each of up to seven R.e¹¹ is a substituent of a ring carbon or a ring heteroatom and:

- is independently selected from saturated or unsaturated, substituted or unsubstituted C₁₋₂₀ branched or straight chain aliphatic, aromatic, alicyclic and combinations thereof, any of which may comprise one or more heteroatoms selected from N, O, S, P, and wherein optional substituents are selected from any C₁₋₁₂ aliphatic, aromatic or alicyclic substituents any of which may comprise one or more heteroatoms as hereinbefore defined, hydroxy, thiol, halo, amine, hydrazine, oxo, cyano, and the like, such as =O, OCH₃, CH₂Ph(OCH₃)₂, O(CH₂)₃CON(CH₃)c.hex, N(CH₂CH₂OH)₂, c.hex, COOCH₂CH₃, CH₂CH₃;
- or any two or more of R.e¹¹ form a one, two or three ring fused cyclic structure, preferably comprising a fused 3 ring aryl, 5-heterocyclic, 6-heterocyclic structure having 4 ring atoms common with the fused bicyclic Lig.e³ structure;
- and R.e¹² is a moiety as defined for R.e¹¹ above;

Preferably Lig.e is of the formula Lig.e¹ as hereinbefore defined in particular where R.e² and R.e³ are respectively propyl and butyl;

-L.e- is suitably as hereinbefore defined for -L.a-.

96. (new). Compound as claimed in claim 95 wherein F1 is selected from the following dyes: Texas red™, coumarin and derivatives, Cascade Blue™, EvoBlue and fluorescent derivatives thereof, pyrenes and pyridyloxazole derivatives, the cyanine dyes, the dyomics (DY dyes and ATTO dyes) and fluorescent derivatives thereof, the Alexafluor dyes and derivatives, BDI dyes including the commercially available Bodipy™ dyes, pyrenes, anthracenes, acridines, fluorescent phycobiliproteins and their conjugates and fluoresceinated microbeads, and Texas Red derivatives, coupled to amine groups using the isocyanate, succinimidyl ester or dichlorotriazinyl-reactive groups.

RESPONSE TO NOTICE OF NON-COMPLIANT AMENDMENT

Application No.: 10/551,475

Attorney Docket No.: Q111431

97. (new and withdrawn). Process for the preparation of a library as claimed in Claim 59, wherein reactive groups Y_{Lig} , Y_L , Y_T have suitable reactive group functionalities for linking by addition or addition – elimination reaction.

98. (new and withdrawn). Process for the preparation of a compound as claimed in Claim 60, wherein reactive groups Y_{Lig} , Y_L , Y_T have suitable reactive group functionalities for linking by addition or addition – elimination reaction.